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AAA: triple adaptive Bayesian designs for the identification of optimal dose combinations in dual-agent dose finding trials

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Summary.

We propose a flexible design for the identification of optimal dose combinations in dual-agent dose finding clinical trials. The design is called AAA, standing for three adaptations: adaptive model selection, adaptive dose insertion and adaptive cohort division. The adaptations highlight the need and opportunity for innovation for dual-agent dose finding and are supported by the numerical results presented in the proposed simulation studies. To our knowledge, this is the first design that allows for all three adaptations at the same time. We find that AAA enhances the chance of finding the optimal dose combinations and shortens the trial duration. A clinical trial is being planned to apply the AAA design and a Web tool is being developed for both statisticians and non-statisticians.

Keywords

Adaptive cohort division; Bayesian inference; Dose combination; Hierarchical models; Markov chain Monte Carlo simulation; Phase I–II clinical trial

1. Introduction

Dual-agent dose finding trials are becoming much more popular in oncology as more new drugs become available. The traditional two-agent dose finding trials often aim to capture the dose– toxicity relationship for the combinations and identify one or more maximum tolerated dose combination (MTDC) of two agents. The MTDC is defined as the highest dose combination at which the probability that a patient experiences the dose limiting

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6. Supplementary materials

Appendices, tables and figures, referenced in Sections 2.3, 2.6, 4.1, 4.2, 4.4 and 5, are available on line with this paper.

toxicity (DLT) is less than a prespecified target rate p_T, which is usually determined by physicians or clinical teams. A large number of designs have been proposed to find the MTDC for trials with cytotoxic agents. For example, Conaway *et al.* (2004) estimated the MTDC by determining the complete and partial orders of the toxicity probabilities by using nodal and non-nodal parameters. Yin and Yuan (2009) introduced Bayesian dose finding approaches using copula regression models. Braun and Wang (2010) developed a novel hierarchical Bayesian design accounting for patients' heterogeneity and Wages *et al.* (2011) applied model selection to estimate possible complete orderings associated with the partial order based on the continual reassessment method. Later, Hirakawa *et al.* (2013) developed a likelihood-based dose finding method using a shrinkage logistic model. As a review, Hirakawa *et al.* (2015) compared these five model-based dose finding designs and found that their performance varied depending on the dose matrix and the location and number of true MTDCs. In addition, on the basis of a four-parameter logistic model, Riviere *et al.* (2014) proposed a Bayesian adaptive design to find the MTDC, Shi and Yin (2013) applied a two-dimensional escalation with overdose control design by searching the MTDC along the rows and columns of the dose matrix, and Tighiouart *et al.* (2014, 2017) reparameterized the logistic model and adopted the conditional univariate escalation with overdose control design to estimate the MTDC curves in a two-dimensional plane and then extended it to three-agents trials to find the MTDC surfaces (Tighiouart *et al.*, 2016). More recently, Mander and Sweeting (2015) published a curve-free method that relied on the product of independent beta probabilities. Sun and Braun (2015) proposed a two-stage adaptive algorithm based on a modified biased coin design. Lin and Yin (2016) developed a Bayesian optimal interval design for dual agents, and Wages (2017) extended the continual reassessment method to identify an MTDC contour for dual agents.

A key assumption in all the works above is the monotonicity of the dose–toxicity response and the dose–efficacy response, which is true in the case of cytotoxic agents (Le Tourneau *et al.*, 2009). As for many new cancer biological or immunological agents, such as chimeric antigen receptors T-cell therapies, the monotonic relationship may not be true, especially for the dose–efficacy relationship (Li *et al.*, 2016). For example, the dose–efficacy curve may follow a non-monotonic pattern, and efficacy may even decrease at higher dose levels (Hoff and Ellis, 2007). Therefore, traditional dose finding designs with a focus on finding the MTDC are not suitable for trials of non-cytotoxic agents. In contrast with the various references for dual cytotoxic agents dose finding, there is a scarcity of designs for non-cytotoxic agents. Instead of identifying the MTDC, one could consider the biologically optimal dose combination (BODC) for biological agents, the definition of which takes into account both efficacy and toxicity. Wages and Conaway (2014) provided a phase I–II adaptive design to find a single dose combination with an acceptable level of toxicity that maximized efficacious response. However, they assumed that the dose–toxicity and dose–efficacy relationships are monotonic among doses of one agent when the dose of another agent is fixed. Cai *et al.* (2014) proposed a novel dose finding algorithm to encourage sufficient exploration of untried dose combinations in the two-dimensional space. Guo and Li (2015) used isotonic regression to estimate partially stochastically ordered marginal posterior distributions of the efficacy and toxicity probabilities to estimate the BODC.

For dual-agent trials, because of the challenges in capturing the proper therapeutic range for the dose levels of both agents, the BODC might locate outside the candidate dose range or sandwiched by existing dose combinations. Therefore, a design that can extrapolate or interpolate a new dose combination when candidate dose combinations are deemed suboptimal can drastically improve one's chance of identifying better dose combinations. For this, Hu *et al.* (2013) considered an adaptive dose insertion scheme to allow new doses to be inserted during the course of a dose finding trial. Later, Chu *et al.* (2016) introduced an extended version. Both methods consider only toxicity outcomes. Guo *et al.* (2015) proposed a toxicity- and efficacy-based dose insertion design with adaptive model selection for single-agent trials and illustrated the importance of correct model specification for dose insertion. They showed that, to insert the right doses, the dose–efficacy relationship must be properly identified.

In this paper, we extend the idea of a toxicity- and efficacy-based dose insertion design with adaptive model selection to dual agents and propose the AAA (triple A) design, which is named after three adaptive features. First, to describe the appropriate dose–efficacy curve, we present an adaptive Bayesian model selection procedure based on median posterior probability models (Barbieri and Berger, 2004) that allows the dose–efficacy model to vary between the monotone pattern and non-monotone pattern. Second, we propose adaptive dose insertion allowing new dose combinations to be extrapolated or interpolated throughout the trial. Last, importantly and innovatively, we consider adaptive cohort division (ACD) and allow multiple cohorts of patients to be enrolled simultaneously during the course of the trial. We show that ACD accelerates trial conduct and shortens trial duration.

We consider a conceived clinical study at the University of Chicago involving an MEK inhibitor and a PIK3CA inhibitor, both with four doses at their regular monotherapy dose, two lower doses and one higher dose. This phase I dose finding study will enrol late stage cancer patients with a primary end point aiming to improve the efficacy rate from 5% to 30% with the optimal tolerated dose combination. Furthermore, a dose combination with improved efficacy rate, say 20% or higher, is considered clinically beneficial as long as the dose is well tolerated. We shall use this study as the basis for our numerical studies later.

The remainder of this paper is organized as follows. In Sections 2 and 3, we describe the probability model and the AAA design. In Section 4, using the phase I trial we examine the operating characteristics of AAA through simulation studies. To evaluate the time reduction by using ACD, we examine the duration of the trial in the simulated trials. We conclude with a discussion in Section 5.

The programs that were used to analyse the data can be obtained from http://wileyonlinelibrary.com/journal/rss-datasets

2. Methods

2.1. Dose–response models

Consider a trial combining J doses of agent A, denoted by $x_{a,1} < \ldots < x_{a,J}$, and K doses of agent B, denoted by $x_{b,1} < \ldots < x_{b,K}$, for dose finding. Without loss of generality, we assume

that $J \geqslant K$ and that the dosage values of the $x_{a,j}$s and $x_{b,k}$s have been standardized to have mean 0 and standard deviation 0.5. Let $\mathbf{x}_{jk} = (x_{a,j}, x_{b,k})$ denote the combination of dose levels j and k, and let $p(\mathbf{x}_{jk})$ and $q(\mathbf{x}_{jk})$ denote probabilities of the toxicity event and efficacy event for the dose combination $(x_{a,j}, x_{b,k})$ respectively, for $j = 1, 2, \ldots, J$, and $k = 1, 2, \ldots, K$.

Assume that $p(\mathbf{x})$ follows a linear logistic model and $q(\mathbf{x})$ follows a quadratic logistic model to incorporate a non-monotone pattern in the dose–efficacy model

$$\text{logit}\{p(\mathbf{x})\} = \alpha_0 + \alpha_1 x_a + \alpha_2 x_b, \quad (1)$$

$$\text{logit}\{q(\mathbf{x})\} = \beta_0 + \beta_1 x_a + \beta_2 x_b + \beta_3 x_a^2 + \beta_4 x_b^2, \quad (2)$$

where $\mathbf{x} = (x_a, x_b)$ is the vector of the dose combination. Later we briefly discuss adding an interaction term $\beta_5 x_a x_b$ in the last section. Denote $\boldsymbol{\alpha} = (\alpha_0, \alpha_1, \alpha_2)'$ and $\boldsymbol{\beta} = (\beta_0, \beta_1, \beta_2, \beta_3, \beta_4)'$ the vector of regression parameters in the dose–toxicity model (1) and dose–efficacy model (2) respectively. Here, we use a working model and assume that the binary outcomes of toxicity and efficacy are independent. This working independence between efficacy and toxicity outcome in dose finding designs has been extensively discussed in the literature (Ivanova *et al.*, 2009; Cai *et al.*, 2014). We also assume that toxicity is monotone with the dose as a conservative choice of model. In other words, $\alpha_1 > 0$ and $\alpha_2 > 0$ in model (1).

2.2. Utility function and definition of biologically optimal dose combination

Utility-based decision criteria have been adopted frequently in recent dose finding trials (Thall and Nguyen, 2012; Lee *et al.*, 2015; Quintana *et al.*, 2016; Li *et al.*, 2016). In this paper, we construct utility functions for dose safety and efficacy evaluation. Denote by $U_T\{p(\mathbf{x}), \eta_0\}$ and $U_E\{q(\mathbf{x}), \tilde{\eta}\}$ the utility for safety and efficacy at dose combination $\mathbf{x} = (x_a, x_b)$ respectively, and define

$$U_T\{p(\mathbf{x}), \eta_0\} = \begin{cases} 1 - \dfrac{1-\eta_0}{p_T} p(\mathbf{x}), & p(\mathbf{x}) \in [0, p_T], \\ 0, & p(\mathbf{x}) \in (p_T, 1], \end{cases} \quad (3)$$

$$U_E\{q(\mathbf{x}), \tilde{\eta}\} = \eta_1 \exp\{\eta_2 q(\mathbf{x})\} + \eta_3, \qquad \eta_2 > 0, \quad (4)$$

where $\tilde{\eta} = (\eta_1, \eta_2, \eta_3)'$. Fig. 1 gives an illustration. Here, the utility for safety U_T in expression (3) is a truncated linear decreasing function with $p(\mathbf{x})$; we assume that the utility U_T decreases with toxicity probability and drops to 0 if $p(\mathbf{x}) > p_T$, i.e. there is no utility when toxicity probability $p(\mathbf{x})$ is larger than p_T. Usually p_T is around 0.3 for oncology trials. The utility for efficacy U_E in equation (4) follows an exponential function with parameters η_1, η_2

and η_3, where $\eta_1 + \eta_3$ decides the utility value when there is no efficacy and (η_1, η_2) decide how fast utility increases when efficacy probability $q(\mathbf{x})$ increases. Combining the utilities for safety and efficacy, we define the overall utility score as

$$U(\mathbf{x}, \theta, \eta) = U_T\{p(\mathbf{x}), \eta_0\}\, U_E\{q(\mathbf{x}), \tilde{\eta}\}, \quad (5)$$

where $\boldsymbol{\theta} = (\boldsymbol{\alpha}', \boldsymbol{\beta}')'$ and $\boldsymbol{\eta} = (\eta_0, \eta_1, \eta_2, \eta_3)'$.

Then the BODC, $\mathbf{x}_{\text{opt}} = (x_{a,\text{opt}}, x_{b,\text{opt}})$, is defined as the dose combination that maximizes the utility function, i.e.

$$\mathbf{x}_{\text{opt}}(\theta) = \underset{\mathbf{x} \in \mathbb{R}^2}{\text{argmax}} \; U(\mathbf{x}, \theta).$$

To specify the unknown values (η_0, η_1, η_2, η_3), we follow a procedure that was suggested by Thall and Cook (2004). We elicit with physicians two pairs of toxicity–efficacy trade-offs, $(0, q_1^*)$ and (p_T, q_2^*), that have the same utility value U^*, *say* $U^* = 0.3$. For example, $q_1^* = 0.1$ and $q_2^* = 0.3$. This gives two equations: $U_T(0, \eta_0) U_E(q_1^*, \tilde{\eta}) = U^*$ and $U_T(p_T, \eta_0) U_E(q_2^*, \tilde{\eta}) = U^*$. In addition, U_T and U_E must have the same scale (0,1), which implies that

a. $U_E\{q(\mathbf{x}) = 0, \tilde{\eta}\} = \eta_1 + \eta_3 = 0$ and

b. $U_E\{q(\mathbf{x}) = 1, \tilde{\eta}\} = \eta_1 \exp(\eta_2) + \eta_3 = 1.$

Therefore, we have a set of four non-linear equations and four unknown parameters. The solution of $\hat{\eta}$ can be easily solved numerically.

2.3. Adaptive model selection for the dose–efficacy model

Efficacy could be either monotone or non-monotone with dose combination, depending on many factors such as the pharmacology and mechanism of action of the drug. Proposing adaptive model selection, we allow adaptation in the model choice throughout the trial. Briefly, when the number of explored dose combinations or the sample size is small, a simpler model, such as a linear logistic model, may fit the data better to avoid the wrong estimation of a dose–response curve due to model misspecification. As the trial proceeds, more dose combinations are explored, more patient data are accumulated and more complex models such as a non-monotone quadratic logistic model might be beneficial to obtain better estimates (Guo *et al.*, 2015).

Consider a model selection framework for the efficacy regression coefficients in equation (2) as follows: model M_1, $\beta_3 = \beta_4 = 0$; model M_2, $\beta_3 \neq 0$, $\beta_4 = 0$; model M_3, $\beta_3 = 0$, $\beta_4 \neq 0$; model M_4, $\beta_3 \neq 0$, $\beta_4 \neq 0$.

Similarly to Guo *et al.* (2015), we adopt inverse moment priors (Johnson and Rossell, 2010) on β_3 under models M_2 and M_4 and on β_4 under models M_3 and M_4, in which cases either or

both of them are assumed to be non-zero. The inverse moment prior has no probability mass at the null point ($\beta_i = 0$, $i = 3, 4$) and takes the form

$$\pi(\beta_i|\mathrm{M}_l) = \frac{k\tau^{\nu/2}}{\Gamma(\nu/2k)}|\beta_i|^{-(\nu+1)}\exp\left(-\frac{\tau^k}{\beta_i^{2k}}\right), \qquad (i,l) \in \{(3,2),(3,4),(4,3),(4,4)\},$$

for k, ν, $\tau > 0$. Some examples of the inverse moment prior are shown in Fig. A.1 in the Web appendix A. The prior when β_3 or β_4 equals 0 is simply a point mass at zero, i.e.

$$\pi(\beta_i|\mathrm{M}_l) = \mathbf{1}\{\beta_i = 0\}, \qquad (i,l) \in \{(3,1),(3,3),(4,1),(4,2)\},$$

where $\mathbf{1}\{\cdot\}$ is the indicator function. With no evidence favouring any of the hypotheses over the others *a priori*, we take $P(\mathrm{M}_1) = P(\mathrm{M}_2) = P(\mathrm{M}_3) = P(\mathrm{M}_4) = \frac{1}{4}$.

In the model selection, we compute $P(\mathrm{M}_l|\text{data})$, the posterior probability of each model, and select the *median probability model* to be the dose–response model. The median probability model is defined as the model consisting of those variables which have overall posterior probability greater than or equal to $\frac{1}{2}$ (Barbieri and Berger, 2004). In our case, denote by p_3 and p_4 the posterior inclusion probability for the quadratic terms x_a^2 and x_b^2 respectively, and define

$$p_3 = P(\mathrm{M}_2|\text{data}) + P(\mathrm{M}_4|\text{data}), \quad (6)$$

$$p_4 = P(\mathrm{M}_3|\text{data}) + P(\mathrm{M}_4|\text{data}), \quad (7)$$

which are also the overall posterior probability that $\beta_3 \neq 0$ and $\beta_4 \neq 0$ respectively. The posterior probability of model M_l, $P(\mathrm{M}_l|\text{data})$ in equations (6) and (7), $l = 2, 3, 4$, is given by

$$P(\mathrm{M}_l|\text{data}) = \frac{P(\text{data}|\mathrm{M}_l)P(\mathrm{M}_l)}{\sum_{l=1}^{4} P(\text{data}|\mathrm{M}_l)P(\mathrm{M}_l)},$$

where $P(\text{data}|\mathrm{M}_l)$ is the marginal distribution of the data under the prior of model M_l, given by

$$P(\text{data}|\mathrm{M}_l) = \int \mathscr{L}(\text{data}|\alpha, \beta_l, \mathrm{M}_l)\,\pi(\alpha, \beta_l|\mathrm{M}_l)\,\mathrm{d}\alpha\,\mathrm{d}\beta_l.$$

Here, $\mathscr{L}(\text{data}|\alpha, \beta_l, \mathrm{M}_l)$ is the likelihood function under model M_l, $l = 1, 2, 3, 4$, $\boldsymbol{\beta}_1 = (\beta_0, \beta_1, \beta_2, \beta_3 = 0, \beta_4 = 0)'$, $\boldsymbol{\beta}_2 = (\beta_0, \beta_1, \beta_2, \beta_3, \beta_4 = 0)'$, $\boldsymbol{\beta}_3 = (\beta_0, \beta_1, \beta_2, \beta_3 = 0, \beta_4)'$ and $\boldsymbol{\beta}_4 =$

$(\beta_0, \beta_1, \beta_2, \beta_3, \beta_4)'$. Since the integral does not have a closed form, numerical integration such as Monte Carlo integration is applied. Specifically, we use the harmonic mean of likelihood values (Kass and Raftery, 1995). Let $\beta_l^{(1)}, \beta_l^{(2)}, \ldots, \beta_l^{(B)}$ be a Markov chain Monte Carlo (MCMC) sample from the posterior distribution of $\boldsymbol{\beta}_l$ under model M_l, suppressing terms that are related to $\boldsymbol{\alpha}$ it can be shown that

$$\int \mathscr{L}(\text{data}\,|\,\beta_l, \mathrm{M}_l)\,\pi(\beta_l|\mathrm{M}_l)\,\mathrm{d}\beta_l \approx \left\{\frac{1}{B}\sum_{b=1}^{B}\mathscr{L}(\text{data}\,|\,\beta_l^{(b)}, \mathrm{M}_l)^{-1}\right\}^{-1},$$

for $l = 1, 2, 3, 4$. Kass and Raftery (1995) showed that the harmonic mean approach is more efficient than directly sampling from the prior, especially when the likelihood function is highly concentrated in an area with low prior probabilities.

We perform model selection based on posterior inclusion probabilities p_3 and p_4 (Table 1). For instance, if $p_3 \geqslant \frac{1}{2}$ and $p_4 \geqslant \frac{1}{2}$, the quadratic terms of both agents x_a^2 and x_b^2 are included in model (2), i.e. $\beta_3, \beta_4 \neq 0$. Therefore, we select model M_4.

2.4. Adaptive dose combination insertion

The therapeutic window of two different drugs is often complex and difficult to delineate. In a trial that prespecifies a set of dose combinations for investigation, a new dose combination should be inserted when the BODC, $\mathbf{x}_{\text{opt}}$, is distant from all the existing dose combinations in the trial. This is our second proposed adaptation. Mathematically, we propose an activation rule for triggering the dose insertion procedure. Let $\mathscr{R}_C(\mathbf{x}_{\text{opt}})$ represent the $C\%$ (e.g. $C = 90\%$) posterior credible circular region of $\mathbf{x}_{\text{opt}}$, defined as

$$\mathscr{R}_C(\mathbf{x}_{\text{opt}}, r) = \left\{(x_{a,\text{opt}}, x_{b,\text{opt}}): \Pr\left\{(x_{a,\text{opt}} - x_{a,0})^2 + (x_{b,\text{opt}} - x_{b,0})^2 \leqslant r\,|\,\text{data}\right\} = C\%\right\},$$

where $(x_{a,0}, x_{b,0})$ and r are the centre and the radius of the circular region respectively. Define A as the indicator of dose insertion:

$$A = \begin{cases} 1, \text{ if } \mathscr{R}_C(\mathbf{x}_{\text{opt}}, r) \cap \left\{(x_{a,j}, x_{b,k}): j = 1, \ldots, J, k = 1, \ldots, K\right\} = \varnothing, \\ 0, \text{ if } \mathscr{R}_C(\mathbf{x}_{\text{opt}}, r) \cap \left\{(x_{a,j}, x_{b,k}): j = 1, \ldots, J, k = 1, \ldots, K\right\} \neq \varnothing, \end{cases} \quad (8)$$

where Ø denotes the empty set. When $A = 1$, the credible region does not cover any existing dose combinations, and the dose insertion procedure is activated. Otherwise, the trial proceeds by treating the next cohort at one of the existing dose combinations.

2.5. Adaptive cohort division

ACD is the third and an innovative adaptation. When two or more doses are considered similarly desirable for the next cohort of patients on the basis of the data collected, the proposed AAA design allows patients to be enrolled simultaneously in parallel cohorts.

The main idea is as follows. When we encounter a toxic dose combination during the trial, a de-escalation is needed that decreases the dose level of either drug. To improve efficiency, we propose to de-escalate to two untried lower dose combinations with parallel patient enrolment at both doses, i.e. we open two cohorts concurrently in this case. Cohorts are collapsed if a new dose combination is inserted, in which case the new single cohort will be enrolled at the inserted dose, or the multiple cohorts all point to the same dose combination for future patients.

Because of the ACD procedure, multiple cohorts can be enrolled at the same time. Some cohorts might finish enrolment and follow-up faster than others. When a cohort finishes follow-up, the efficacy and toxicity response data of the patients in the cohort are observed. At this point, a decision must be made about the next dose combination for future patients. However, at that moment, other cohorts might still be enrolling, or some patients might still be followed up without outcome data whereas others might have completed follow-up with outcomes. To use the existing information fully, we include the patients with complete data in all cohorts in the inference and decision making. In other words, we make a decision on the next dose combination based on the response data from all completers from all cohorts. This achieves faster enrolment and exploration of the new dose combinations, thereby shortening trial duration. A future plan is to model time-to-event outcomes so that information from those patients who are still being followed up can be incorporated in the statistical inference.

2.6. Likelihood and prior specification

Consider the moment when a cohort of patients completes the follow-up during the course of the trial. Let y_{jk} and z_{jk} be the numbers of patients treated at dose combination $(x_{a,j}, x_{b,k})$ with toxicity and efficacy events respectively, and let n_{jk} be the total number of patients treated at the same dose combination, for $j = 1, 2, \ldots, J$, and $k = 1, 2, \ldots, K$. Note that these numbers include all completers in all cohorts. Recall that we assume independence of toxicity and efficacy; for the observed data $\equiv \{(y_{jk}, z_{jk}, n_{jk}), j = 1, 2, \ldots, J, k = 1, 2, \ldots, K\}$, the likelihood function under model M_l is the product of the binomial densities, i.e.

$$\mathscr{L}(\text{data}\,|\,\alpha, \beta_l, \mathrm{M}_l) \propto \prod_{j=1}^{J}\prod_{k=1}^{K} p(\mathbf{x}_{jk}|\alpha)^{y_{jk}}\left\{1 - p(\mathbf{x}_{jk}|\alpha)\right\}^{n_{jk}-y_{jk}} q(\mathbf{x}_{jk}|\beta_l)^{z_{jk}}\left\{1 - q(\mathbf{x}_{jk}|\beta_l)\right\}^{n_{jk}-z_{jk}}$$

where $l = 1, 2, 3, 4$ indexes four different models. Denote $\pi_{\mathrm{E}}(\boldsymbol{\beta}_l|\mathrm{M}_l)$ and $\pi_{\mathrm{T}}(\boldsymbol{\alpha})$ the priors for $\boldsymbol{\beta}_l$ and $\boldsymbol{\alpha}$. Assuming prior independence between $\boldsymbol{\beta}_l$ and $\boldsymbol{\alpha}$, the joint conditional posterior of the parameters under model M_l is given by

$$\pi(\theta_l|\text{data}, \mathrm{M}_l) \propto \mathscr{L}(\text{data}\,|\,\alpha, \beta_l, \mathrm{M}_l)\,\pi_{\mathrm{E}}(\beta_l|\mathrm{M}_l)\pi_{\mathrm{T}}(\alpha),$$

where $\theta_l = (\alpha', \beta_l')'$.

For the prior specification of parameters in the efficacy model (2) other than β_3 and β_4, we use a weakly informative prior for β_0, β_1 and β_2, recommended by Gelman *et al.* (2008).

Specifically, $\beta_0 \sim$ Cauchy(0, 10), and $\beta_1, \beta_2 \sim$ Cauchy(0, 2.5), where Cauchy (c, d) denotes a Cauchy distribution with centre parameter c and scale parameter d. These weakly informative and appropriately regularized priors improve the stability of the estimation and still ensure that the data can dominate the priors (Gelman *et al.*, 2008). For the inverse moment priors for β_3 and β_4, we use the default values for k and ν, $k = \nu = 1$, recommended by Johnson and Rossell (2010). With respect to the choice of parameter τ, we finally decide to set $\tau = 5$ on the basis of the technical details shown in the Web appendix A.

For the toxicity model (1), we also adopt the weakly informative prior Cauchy(0, 10) for intercept α_0. We assign α_1 and α_2 independent gamma distributions with the shape parameter of 0.5 and the rate parameter of 0.5. This gives mean 1 and variance 2.

3. Trial design

3.1. Overview

The dose finding design proposed consists of two stages. Stage I is a run-in period, in which we escalate the dose along the diagonal of the dose combination matrix to explore the dose combination space quickly and to collect preliminary data for stage II. Specifically, in stage I we make dose escalation decisions based on the mTPI-2 design (Guo *et al.*, 2017). There are three possibilities. First, if mTPI-2 gives the 'escalate' decision based on the toxicity outcomes of the current dose combination $\mathbf{x}_{jk}$, ($y_{j,k}$, $n_{j,k}$), dose escalation along the diagonal will be allowed, i.e. the next cohort of patients will be treated at dose combination $\mathbf{x}_{j+1,k+1}$. Second, if mTPI-2 gives 'stay', the trial stays at the current dose $\mathbf{x}_{jk}$ and enrols more patients until up to nine patients have been enrolled and treated at this dose; at that point stage II starts. Third, if mTPI-2 gives 'de-escalate', stage I stops and stage II starts. If the dose matrix is not square (i.e. $J > K$), after first escalating the dose along the diagonal to ($x_{a,K}$, $x_{b,K}$), we escalate the dose by holding the dose level of agent B at K and increasing the dose level of agent A from ($x_{a,K}$, $x_{b,K}$) to ($x_{a,K\,1}$, $x_{b,K}$) and so on. After stage I, the trials enters stage II: adaptive dose finding.

In stage II, we apply the toxicity and efficacy probability models for inference, the utility function for dose assessment and the three adaptive procedures (model selection, dose insertion and cohort division) in Section 2 for adaptive dose finding. A simple flow chart in Fig. 2 depicts the flow of stage II in AAA. Specifically, once a cohort of patients has completed follow-up in the trial, we update the recorded outcome data from existing doses and enrolled patients, generate MCMC posterior samples of the parameters under models M_1, M_2, M_3 and M_4 respectively, denoted by $\left\{\theta_l^{(b)}, b = 1, 2, \ldots, B\right\}$, $l = 1, 2, 3, 4$, and carry out adaptive model selection based on the median probability model by using the updated data. Suppose that model M_{l*} is selected: we obtain an MCMC posterior sample of θ_{l*} under the selected model M_{l*}. For each simulated values $\theta_{l*}^{(b)}$ from the bth MCMC iteration, $b = 1, 2, \ldots, B$, we maximize the utility function $U(\mathbf{x}, \theta_{l*}^{(b)})$ with respect to dose combination $\mathbf{x}$, to obtain a posterior sample of BODC, i.e.

$$\hat{\mathbf{x}}^{(b)}_{\text{opt},\,l*} = (\hat{x}^{(b)}_{a,\,\text{opt},\,l*}, \hat{x}^{(b)}_{b,\,\text{opt},\,l*}) = \underset{\mathbf{x}\,\in\,\mathbb{R}^2}{\text{argmax}}\;\; U(\mathbf{x}, \theta^{(b)}_{l*}), \qquad l* \in \{1,2,3,4\}\,. \quad (9)$$

Then the posterior mean of BODC is

$$\hat{\mathbf{x}}_{\text{opt}} = (\hat{x}_{a,\,\text{opt}}, \hat{x}_{b,\,\text{opt}}) = \sum_{b\,=\,1}^{B} \hat{\mathbf{x}}^{(b)}_{\text{opt},\,l*}/B\,.$$

3.2. Deciding the next dose combination

We first consider whether dose insertion is needed on the basis of the estimation of A in equation (8). Specifically, using the posterior sample of BODC $\{\hat{\mathbf{x}}^{(b)}_{\text{opt},\,l*}: b = 1, 2, \ldots, B\}$, let

$$\begin{aligned}\hat{A} &= \mathbf{1}\{\Pr\{(x_{a,\,\text{opt},\,l*} - \hat{x}_{a,\,\text{opt}})^2 + (x_{b,\,\text{opt},\,l*} - \hat{x}_{b,\,\text{opt}})^2 \leqslant \hat{r}\} > C\%\} \qquad (10)\\ &\approx \mathbf{1}\{\frac{1}{B}\sum_{b}\mathbf{1}\{x^{(b)}_{a,\,\text{opt},\,l*} - \hat{x}_{a,\,\text{opt}})^2 + (x^{(b)}_{b,\,\text{opt},\,l*} - \hat{x}_{b,\,\text{opt}})^2 \leqslant \hat{r}\} > C\%\},\end{aligned}$$

where $\mathbf{1}\{\cdot\}$is the indicator function and $\hat{r}$ is the minimum Euclidean distance among the distances between the centre and the existing dose combinations, denoted by

$$\hat{r} = \min_{j,\,k}[\sqrt{\{(x_{a,\,j} - \hat{x}_{a,\,\text{opt}})^2 + (x_{b,\,k} - \hat{x}_{b,\,\text{opt}})^2\}}]\,.$$

We can easily see that $\hat{A}$ in approximation (10) is a posterior estimate of equation (8).

If dose insertion is needed, i.e. $\hat{A} = 1$, we insert the new dose combination $(\hat{x}_{a,\,\text{opt}}, \hat{x}_{b,\,\text{opt}})$ and two sets of new dose combinations

$$\left\{(x_{a,\,1}, \hat{x}_{b,\,\text{opt}}),\ \ldots, (x_{a,\,J}, \hat{x}_{b,\,\text{opt}})\right\}$$

and

$$\left\{(\hat{x}_{a,\,\text{opt}}, x_{b,\,1}),\ \ldots, (\hat{x}_{a,\,\text{opt}}, x_{b,\,K})\right\}$$

into the dose combination matrix, as shown in Fig. 3 and assign the next cohort to the new dose combination $(\hat{x}_{a,\,\text{opt}}, \hat{x}_{b,\,\text{opt}})$.

If dose insertion is not needed, i.e. $\hat{A} = 0$, we assign the next cohort of patients according to the utility of the existing dose combinations. Let N denote the prespecified maximum sample size, n_1 the number of enrolled patients in stage I and $N_2 = N - n_1$ the total number

of patients who are available for stage II. Given the current dose combination $\mathbf{x}_{jk} = (x_{a,j}, x_{b,k})$, we define the one-degree admissible dose set, denoted by $\mathscr{A}_1$, as the dose combination $\mathbf{x}_{j'k'}$,whose dose levels are no more than 1 level different from $\mathbf{x}_{jk}$ and satisfy the safety requirement, i.e. $\mathscr{A}_1 = \left\{\mathbf{x}_{j'k'} : |j' - j| \leqslant 1, |k' - k| \leqslant 1, \Pr\left\{p(\mathbf{x}_{j'k'}) > p_T | \text{data}\right\} \leqslant \xi\right\}$, where ξ is close to 1. Hereinafter, a dose combination is considered overly toxic and unacceptable if it satisfies $\Pr\{p(\mathbf{x}_{jk}) > p_T|\text{data}\} > \xi$, where ξ is close to 1. If not unacceptable, then a dose combination is acceptable. Then the next dose combination is decided on the basis of the following algorithm.

If $(x_{a,j}, x_{b,k})$ is considered acceptable, assign patients as follows.

a. On the basis of the accumulated trial data, determine dose set $\mathscr{A}_1$.

b. Among the dose combinations in $\mathscr{A}_1$, compute the posterior mean utility for each combination, i.e. $\bar{U}(\mathbf{x}_{j'k'}, \theta_{l^*}) = (1/B)\sum_{b=1}^{B} U(\mathbf{x}_{j'k'}, \theta_{l^*}^{(b)})$, $\mathbf{x}_{j'k'} \in \mathscr{A}_1$, and identify the dose combination $\mathbf{x}_{j^*k^*} = (x_{a,j^*}, x_{b,k^*})$ with the highest posterior mean utility under the safety constraint $j^* - j + k^* - k \leqslant 1$, i.e.

$$\mathbf{x}_{j^*k^*} = \underset{\mathbf{x}_{j'k'}}{\text{argmax}}\{\bar{U}(\mathbf{x}_{j'k'}, \theta_{l^*})\}, \quad \text{subject to } \mathbf{x}_{j'k'} \in \mathscr{A}_1 \text{ and } j' - j + k' - k \leqslant 1. \quad (11)$$

c. If dose combination $\mathbf{x}_{j^*k^*}$ has not been used to treat any patient thus far, or all doses in $\mathscr{A}_1$ have been used to treat patients, we assign the next cohort of patients to $\mathbf{x}_{j^*k^*}$. However, if $\mathbf{x}_{j^*k^*}$ has been used and there are some untried dose combinations in $\mathscr{A}_1$, we assign the next cohort of patients to $\mathbf{x}_{j^*k^*}$ only if

$$\widehat{\Pr}\{U(\mathbf{x}_{j^*k^*}, \theta_{l^*}) > U_0|\text{data}\} \approx \frac{1}{B}\sum_{b=1}^{B} \mathbf{1}\{U(\mathbf{x}_{j^*k^*}, \theta_{l^*}^{(b)}) > U_0\} > \left(\frac{N_2 - n_2}{N_2}\right)^{\omega}$$

where U_0 is the lowest acceptable utility value, n_2 is the total number of patients that have been treated in stage II and ω is a known tuning parameter controlling how stringent the threshold is. Otherwise, exclude $\mathbf{x}_{j^*k^*}$ from $\mathscr{A}_1$ and return to step (b).

If $(x_{a,j}, x_{b,k})$ *is considered unacceptable*, de-escalate to the untried one-degree lower doses, $\mathbf{x}_{j-1,k} = (x_{a,j-1}, x_{b,k})$ or $\mathbf{x}_{j,k-1} = (x_{a,j}, x_{b,k-1})$ or both, i.e., if both dose combinations exist and have not been used, two cohorts of patients are recruited and assigned to $(x_{a,j-1}, x_{b,k})$ and $(x_{a,j}, x_{b,k-1})$, simultaneously. If only one dose exists and has not been used, assign the next cohort of patients to this dose. If both doses exist but both have been used, terminate this cohort and do not recommend any dose for the next cohort until there is a cohort newly completed.

As seen above, we adopt a concept of one-degree admissible neighbour $\mathcal{A}_1$ in assigning the next dose combinations when dose insertion is not needed. Cai *et al.* (2014) demonstrated that this admissible neighbour and adaptive rule (step (c)) not only encourage the exploration of untried dose combinations to avoid the problem of trapping in suboptimal doses, but also restrict the dose escalation–de-escalation within the neighbours of the current dose, avoiding dramatic dose changes and improving the reliability of the dose finding. Because of the ACD, two or more cohorts might complete follow-up and we might have two or more 'current dose combinations' available. In this case, we apply the above algorithm to each dose combination separately.

3.3. Dose-finding algorithm

AAA's design is summarized in Table 2. Additional rules listed in Table 3 are for ethics and stability concern. For brevity, we use 'dose' to denote a dose combination hereinafter.

A trial should be terminated if dose extrapolation is not activated (because of lack of information, for example, at the beginning of the trial) but the lowest dose is deemed overly toxic. Therefore, we need rule 2 to terminate the trial early because of toxicity when dose insertion is not activated.

4. Simulation

4.1. Simulation set-up

We consider the motivating trials combining two agents, an MEK inhibitor and a PIK3CA inhibitor, each with four dose levels. The maximum sample size is 96 and the cohort size is 3. We investigate 11 different scenarios, and all scenarios assume a true linear or quadratic logistic model for both agents in the dose–efficacy relationship, as shown in Fig. 4 and Fig. C.2 (Web appendix C). For each scenario, 1000 simulated trials are conducted. In the design proposed, we set the BODC target toxicity rate $p_T = 0.3$, the credible level threshold $C\% = 90\%$, the lowest acceptable utility value $U_0 = 0.1$ and the tuning parameter $\omega = 2$. The probability threshold ξ 0.95 for the practical rule and safety requirement. Regarding the utility function, we assume that the two toxicity and efficacy rate pairs (0,0.45) and (0.3,0.85) have the same utility value 0.3. As a result, we obtain the estimated $\hat{\eta} = (0.369,\ 0.385,\ 1.280,\ -0.385)$. Note that, under this configuration of $\hat{\eta}$, a dose combination with toxicity and efficacy rates (0, 0.2) would result in an efficacy utility value of 0.11, which is higher than U_0, i.e. we aim to find dose combinations with at least 20% efficacy rate. This decision is reached after discussion with our clinical collaborators. For different trials, one can go through a similar exercise to elicit U_0- and $\boldsymbol{\eta}$-values.

For MCMC computation, we adopt a standard random-walk Metropolis–Hastings algorithm. And, for each chain, 10000 MCMC samples are drawn with a burn-in size of 5000 iterations. The MCMC algorithm mixed fast and well with no sign of problems of convergence.

For comparison, we apply the design in Cai *et al.* (2014). For fairness, we slightly modified this design by using the utility function rather than efficacy probability for defining the admissible dose set $\mathcal{A}_1$. This typically improved the performance of their design on the basis

of our experience. There is no dose insertion and model selection in their algorithm. Therefore, we compare only dose allocation and dose selection. To demonstrate the benefit of ACD, we turn off the ACD procedure in AAA and apply a single-cohort algorithm, in which we randomly select one dose in step II(c) if two doses are available for ACD. See the Web appendix B for details of the simulation scheme for patient enrolment and follow-up.

4.2. Operating characteristics

The operating characteristics of the proposed algorithm for scenarios 1–6 are summarized in Figs 4 and 5 and Table 4. The two figures include the galaxy plots that present patient allocation and frequency of BODC recommendation respectively. Also, the true BODC, insertion rate and estimated dose levels of the doses inserted and selected BODCs at the end of the trial are provided at the top of each scenario-specific galaxy plot. Table 4 has six sections per scenario. The first section gives a brief description of the true dose response and the need for insertion. The next two sections provide the mean (and standard deviation in parentheses) of the posterior means across the 1000 simulated trials for the regression parameters in the dose–toxicity and dose–efficacy models. The fourth section summarizes the model selection frequencies. The fifth section lists the prespecified dose levels, the true toxicity and efficacy probabilities and utilities of all the doses. The last section measures the safety of the trial in terms of early termination, overall DLT rate and the percentage of trials with DLT rate greater than $p_T = 0.3$ for both AAA and the design in Cai *et al.* (2014).

In scenario 1, the efficacy rates firstly increase and decrease later with both agents. The true BODC $\mathbf{x}_{opt}$ = (0.517, 0.531) is bracketed by doses (0.4, 0.4), (0.4, 0.7), (0.7, 0.4) and (0.7, 0.7) (Fig. 4). From Fig. 4, we see that AAA inserts new doses with mean (0.512, 0.518) in 42.8% of the simulated trials. The utility of the mean inserted dose combination under the true model is 0.445, which is higher than that of all prespecified dose combinations. Among all the patients, 16.3% are treated at the inserted new dose combinations. At the end of 41.1% of the simulated trials, an inserted dose is claimed to be the BODC (Fig. 5). The mean selected BODC at the end of the trial is (0.504, 0.518), which is close to the true BODC. Also, 88.1% of the trials correctly choose the quadratic logistic regression for both agents for the dose–efficacy curve at the end, and the posterior sample means of $\boldsymbol{\beta}$ are close to the true values (Table 4). Figs D.4 and D.6 (Web appendix D) present results of Cai *et al.* (2014) in terms of patient allocation and dose selection. The results are reasonable as most patients are allocated to the four doses that surround the true BODC. However, since their design does not allow dose insertion, it cannot correctly identify the true BODC.

Scenario 2 has a similar pattern of dose–toxicity and dose–efficacy curves to that of scenario 1. From Figs 4 and 5, there is no need for insertion. AAA inserts new doses in only 9.1% of trials. The mean selected dose combination is (0.405, 0.402), which is close to the true BODC (0.408, 0.404).

Scenario 3 reflects a setting where only a few doses are tolerable whereas others are overly toxic (Figs 4 and 5). Because the utility of the existing dose $\mathbf{x}_{22}$ = (0.4, 0.4) is 0.26, which is not much different from the utility of the true BODC (0.468, 0.409), 0.283, only 37.9% of the trials insert new doses. At the end of 1000 simulated trials, AAA selects the true quadratic logistic model for the dose–efficacy 77.7% of the time. AAA shows a higher

toxicity profile than that of Cai *et al.* (2014). The main reason is because, when ACD is invoked at dose (0.7, 0.7), AAA would de-escalate simultaneously to dose (0.4, 0.7) and (0.7, 0.4) if they are untried. However, both doses are above the MTDC, therefore resulting in more toxicity outcomes. In contrast, the approach of Cai *et al.* (2014) is more likely to de-escalate to dose (0.4, 0.4) if (0.7, 0.7) is deemed overly toxic. However, the behaviour of AAA is acceptable since, in the real world, it is impossible to know how toxic an untried lower dose is and, by encouraging exploration of those untried lower doses by using ACD, the trial gains in the speed of the trial conduct (Table 5) and power of identifying the BODC (70.5% *versus* 37.2%, AAA *versus* Cai).

Scenario 4 is a situation when all combinations are higher than the MTDC, and hence 2.6% of the trials are terminated at an early stage according to practical rule 2. New dose combinations with a mean (−0.277,−0.214) are inserted among 99.8% of the completed trials, and 99.2% end with selecting new dose combinations as the BODC. The mean selected dose combination is (−0.283, −0.175) whereas the true BODC is (− 0.313, −0.195) (Figs 4 and 5). This scenario demonstrates the important safety feature of the design proposed. Also, AAA not only stops the trial early because of toxicity, but it also performs desirable dose insertion below all the prespecified doses and identifies the correct BODC.

Unlike the previous four scenarios, scenario 5 presents a situation where the prespecified dose matrix covers only the bottom left-hand corner of the quadratic dose–efficacy curve. Thus, the efficacy grows with both agents and the true BODC (1.203, 1.219) locates at the upper right-hand corner beyond the dose matrix (Figs 4 and 5). The insertion rate is 26.9%, and the mean inserted dose and selected BODC are (0.491, 0.4) and (0.902, 0.84), which are poorly estimated. And all four dose–efficacy models are selected at similar rates. There are two reasons. First, because the prespecified doses do not cover a wide range of dose–response surface, and few patients are allocated to the lower left-hand corner of the dose matrix because of their futility (Fig. 4), data on these doses could not provide a good estimate of the entire curve. Second, with a relatively small sample size $N = 96$, the simulated trials often run out of patients before the BODC has been reached. If a large N is allowed, the dose matrix could be extrapolated well and the dose insertion algorithm would perform better (the results are not shown). However, AAA still allocates most patients (24.8%) to the highest dose that is closest to the true BODC and selects it most often (46.4%) at the end of the trial.

Scenario 6 assumes that the true dose–efficacy model is a linear logistic model. About 29.8% of the simulated trials insert new doses, and the linear model is selected at a relatively high rate, 62%. A total of 23.2% of trials select the inserted doses as the BODC with mean (1.127, 0.21), and the mean selected dose combination is (0.99, 0.322).

The results of scenarios 7–11 are given in Figs C.2, C.3 and Table C.1 in the Web appendix C. Scenario 7 shows the same pattern as scenario 1 but with a flat efficacy curve and low efficacy rates (0.2 or less). At the end of 1000 simulated trials, 58.9% select the quadratic dose–efficacy model for both agents and 28.5% insert new doses. A total of 12.4% of patients are treated at the inserted dose and 19.9% trials select the inserted dose at the end with a mean of (0.487, 0.505), which is close to the true BODC (0.519, 0.528). In scenarios

8–11, the dose–efficacy curves increase first and fall later with one agent but are monotone with another agent. In addition, the true BODCs are all outside the prespecified dose matrix at the right-hand side, top side, left-hand side and bottom side regions respectively. In all four scenarios, insertion is needed, and the insertion rates for AAA are 28.6%, 37.7%, 30.6% and 40.1% respectively. The mean selected doses are close to the true BODCs in all four scenarios.

After careful comparison of results in Figs 4 and 5, and C.2 and C.3 (in the Web appendix C) for AAA, and Figs D.4–D.7 (in the Web appendix D) with those for Cai *et al.* (2014), we find that AAA assigns more patients to doses near the true BODC and selects these doses with higher frequencies. These improvements are potentially due to the three proposed adaptive features. Therefore, we believe that all three features or a subset of them can be used as an add-on to existing designs, such as that in Cai *et al.* (2014), to improve the performance of these methods.

4.3. Time duration

Table 5 demonstrates the benefit of ACD in shortening trial duration. In particular, step II(c) in Table 2 is expected to speed up the trial process and to reduce the time duration. It can be seen from Table 5 that about 40 days can be saved across most scenarios with the ACD procedure. The trial is never longer with ACD than without ACD. Scenarios with more toxic doses result in more reduction of trial time. For example, for scenario 3, the trial duration is reduced by about 90 days. However, if all doses are overly toxic or acceptable, the reduction of time duration is negligible, since cohort division is not allowed for inserted doses. The performances of multiple cohorts and single cohorts are almost the same in terms of the mean selected BODC, patient allocation and the percentage of being selected as the BODC.

4.4. Sensitivity to sample size

Lastly, to evaluate the effect of sample size, we apply the algorithm with a smaller sample size of 66 to scenarios 1, 4 and 5. Results are summarized in Figs E.8, E.9 and Table E.2 in the Web appendix E. We find that the reduction of sample size has a larger influence on scenario 1 than on scenarios 4 and 5. Specifically, for scenario 1, the insertion rate is reduced to 27% (from 42.5%) and the proportion of selecting the correct quadratic model is declined to 83.4% (from 88.1%), although the mean inserted dose combination (0.503, 0.504) and the mean selected BODC (0.502, 0.525) are still close to the truth. In other words, reduction in sample size seems to affect dose insertion, but dose selection not much at the end.

5. Discussion

We propose a new Bayesian adaptive dose insertion design for dual-agents phase I–II oncology trials. The dose insertion procedure based on both efficacy and toxicity enables us to locate more desirable dose combinations. Bayesian model selection during the trial enables the dose–efficacy relationship to be adapted between linear and quadratic logistic models. The model selection has been shown to be important (Guo *et al.*, 2015) in dose insertion and maintaining a high efficiency of the dose finding trial. ACD speeds up the trial

process and shortens the time duration in most scenarios. Simulation results show that the design proposed has desirable operating characteristics.

The AAA design is a utility-based method. Clearly, the performance heavily depends on the definition of utility. Although we choose utility as a multiplication of a linear truncated function (safety utility) and an exponential function (efficacy) in this paper, one can use other reasonable alternative utilities. Choosing an appropriate utility function must be done for individual trials and through discussion between clinicians and statisticians. For different diseases and drugs, a different trade-off between efficacy and toxicity might be allowed. Nevertheless, changes in the utility function are a separate topic and do not affect the overall statistical design illustrated in Tables 2 and 3. In other words, the algorithm that is presented therein is expected to find the optimal dose combination with high likelihood on the basis of the defined utility, however it is defined.

In AAA, we consider model selection so that linear and quadratic efficacy–response curves will be explicitly selected against each other. We could investigate model misspecification for other shapes, such as probit, Emax and change point models. On the basis of our previous experience (Guo *et al.*, 2015), the operating characteristics of the type of designs like AAA should not be highly sensitive to model misspecification partially because of the discrete doses that are used in these trials and partially because of the goal of finding candidate BODCs instead of estimating the whole dose–response curves. Also, Guo *et al.* (2015) investigated Bayesian model averaging instead of Bayesian model selection in the case of dose finding designs. They showed that both approaches led to similar operating characteristics. Apparently, if one is interested in the actual dose–response shape, then model selection would be the choice for inference.

Dose extrapolation and dose interpolation are necessary to identify the BODC when candidate dose combinations are deemed suboptimal. To insert an appropriate dose, two points should be noted: one is the insertion criterion and another is the insertion frequency. In the AAA design, dose insertion is activated by formula (10). On the basis of a stringent value of C% (say, 90%), AAA only inserts new dose combinations with high confidence and low frequencies (see Fig. F.10 in the Web appendix F). Also, the range of dose inserted levels can be decided on the basis of previous animal data and discussion with the clinical team. One can certainly add another criterion to forbid dose insertion if the utility of the dose inserted is not better than the maximum utility of existing doses by a certain percentage. We did not do this simply because the current criterion works well in the simulation. We use simple upper and lower limits for dose extrapolation in rule 1 in Table 3, although these limits can be easily adjusted.

In AAA, inference for dose allocation is based on the complete data from enrolled patients, i.e. we do not use the partial information (e.g. time to event) from patients who are still being followed without outcomes. As a future extension, we plan to construct a time-to-event model, like TITE-CRM (Cheung and Chappell, 2000), or to apply data augmentation to impute the missing outcomes, like Jin *et al.* (2014).

In our models, we do not include an interaction effect $\beta_5 x_a x_b$ for the two agents for a couple of reasons. First, in phase I dose finding trials, an interaction effect is often added depending on preclinical knowledge of the two agents, such as strong evidence on pharmacology and mechanism. When such knowledge is available, we recommend directly adding an interaction in the model rather than performing model selection since the power for identifying interaction based on trial data would be low. Second, it has been demonstrated that, for dose finding, a local fit with a working model of the response surface does not affect the efficiency of dose finding much, i.e., even when models are misspecified (by not including a true interaction term), the dose finding decisions may not be severely affected. This has been shown in Cai *et al.* (2014) and Wang and Ivanova (2005) in the context of drug combination trials. To see this, we simulated two scenarios consisting of the interaction term $\beta_5 x_a x_b$ and fitted data by using dose– efficacy models either with or without the interaction term. The results are summarized in Figs G.11 and G.12, and Table G.3 in the Web appendix G. We can see that AAA can still locate the BODCs well although the inference on parameter estimates and dose insertion is not as accurate when compared with results for scenarios 1 and 6. In addition, an efficacy model without the interaction term can even outperform models with the interaction term (Figs G.11 and G.12), which suggests that adding an interaction term when the number of dose combinations and sample size are relatively small may hurt the inference. This has also been noted in Cai *et al.* (2014) and Wang and Ivanova (2005). We give a brief explanation next. Note that accurate estimation of β_5 is needed for model selection, which in turn requires a large sample size and well-placed dose combinations across the dose–response surface. This is not so for the scenarios in this simulation. We found that, when we increased to a combination of 6×6 or 7×7 dose levels, the interaction can be well estimated (the results are not shown).

A futility stopping rule can be added as part of practical rules in Table 3. For example, if the posterior probability that the efficacy rate of the estimated optimal dose is lower than a cut-off rate is higher than ξ, the trial can be stopped early for futility.

The AAA design is quite complex and requires information technology support for practical deployment. For example, a central information system and electronic data capture are required for smooth operation in real life settings. The design needs to be embedded in the information system to provide decisions based on electronic data. Also, the entire clinical and statistical team needs to meet regularly to review and approve the dose finding decisions. However, these operations are now routinely conducted for adaptive clinical trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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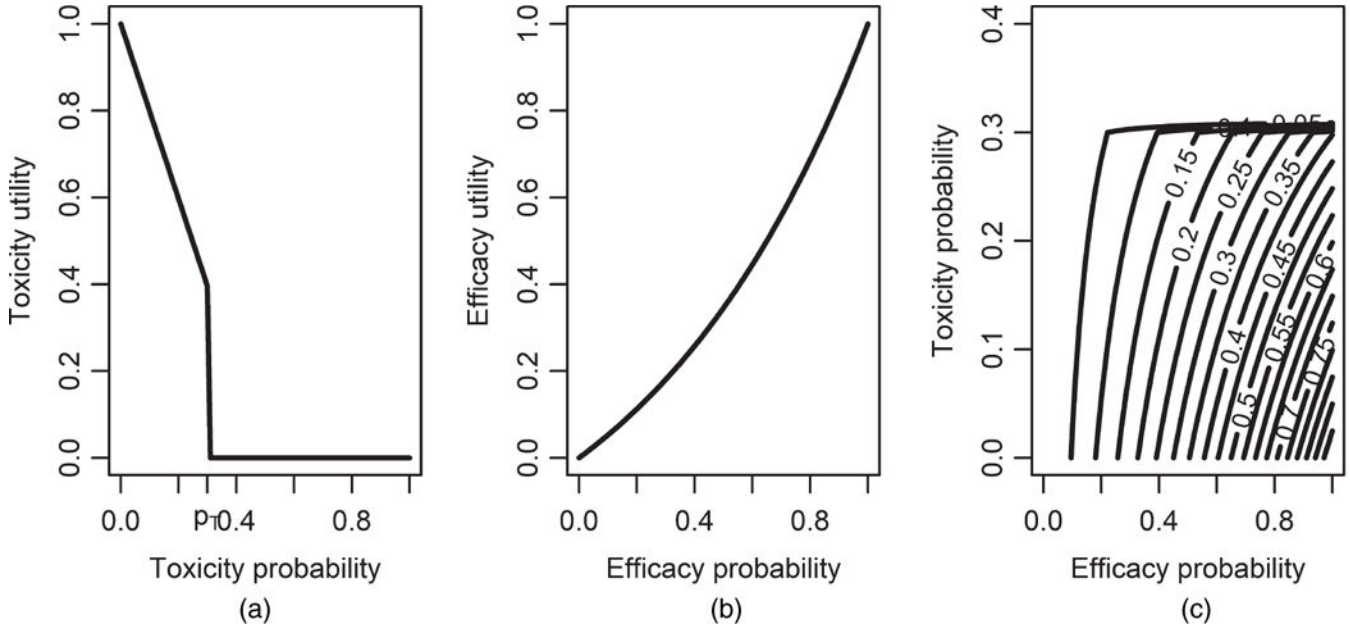

Fig. 1.

Utility functions: (a) utility for safety (truncated at pT and sharply decreases to 0), (b) utility for efficacy and (c) overall utility contours

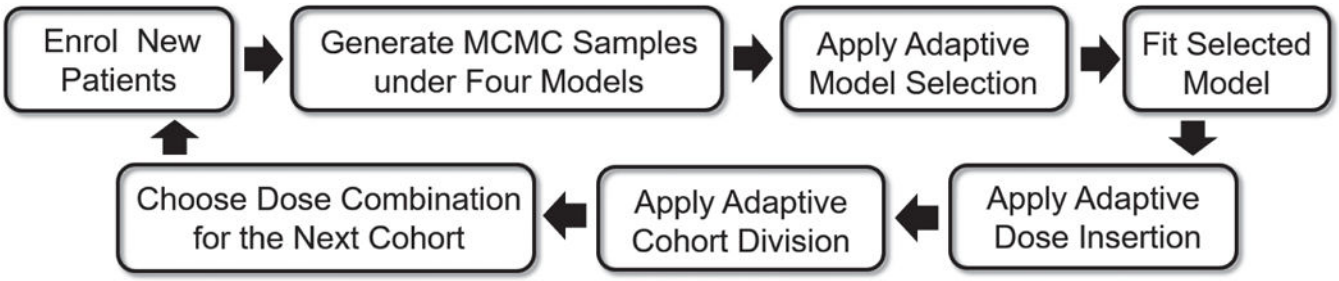

Fig. 2.
Simple flow chart for stage II in the AAA design

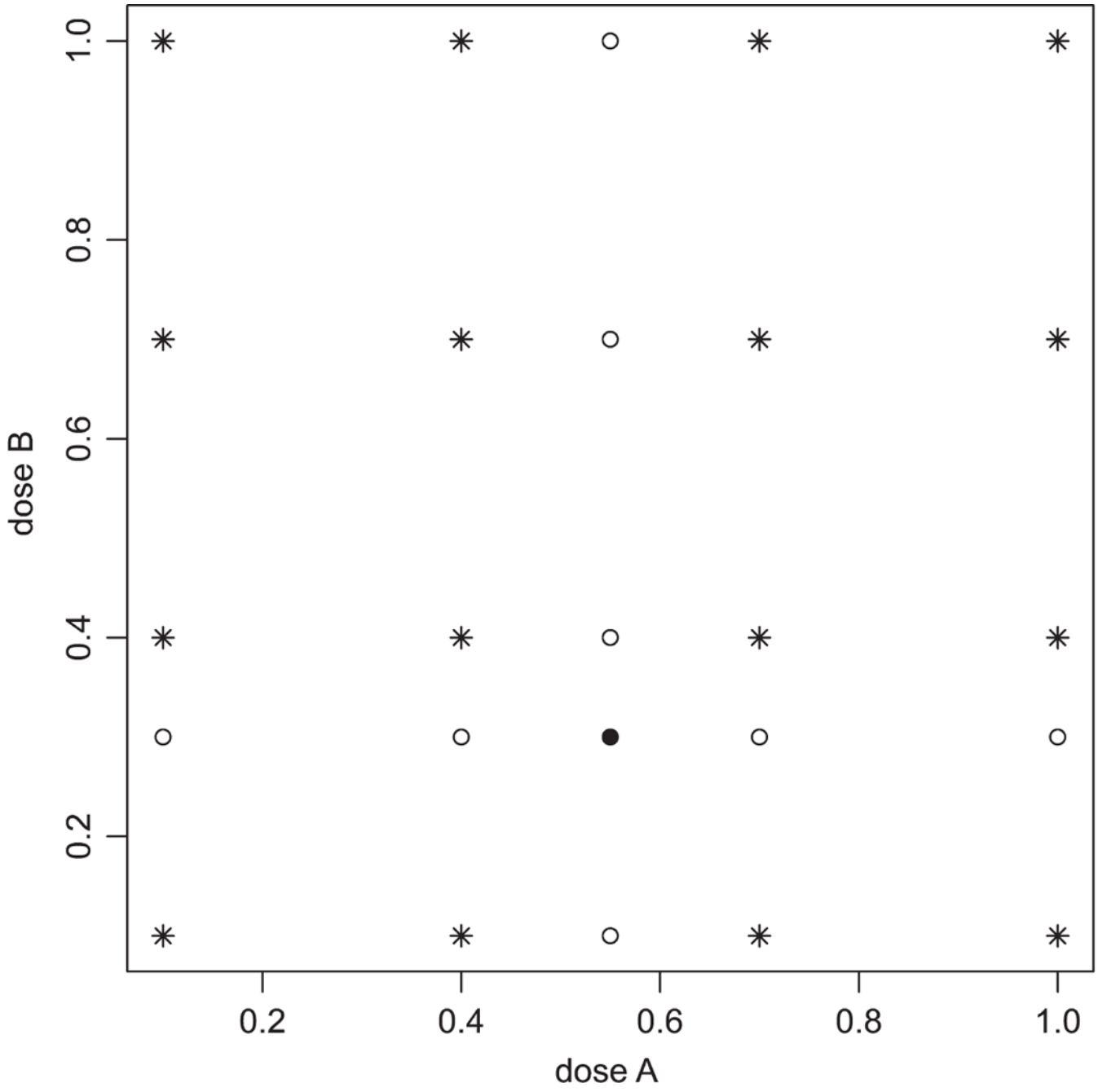

Fig. 3.

Procedure of dose insertion: *, prespecified dose combinations; ○, inserted dose combinations; ●, inserted optimal $(\hat{X}_a, \hat{X}_b)$

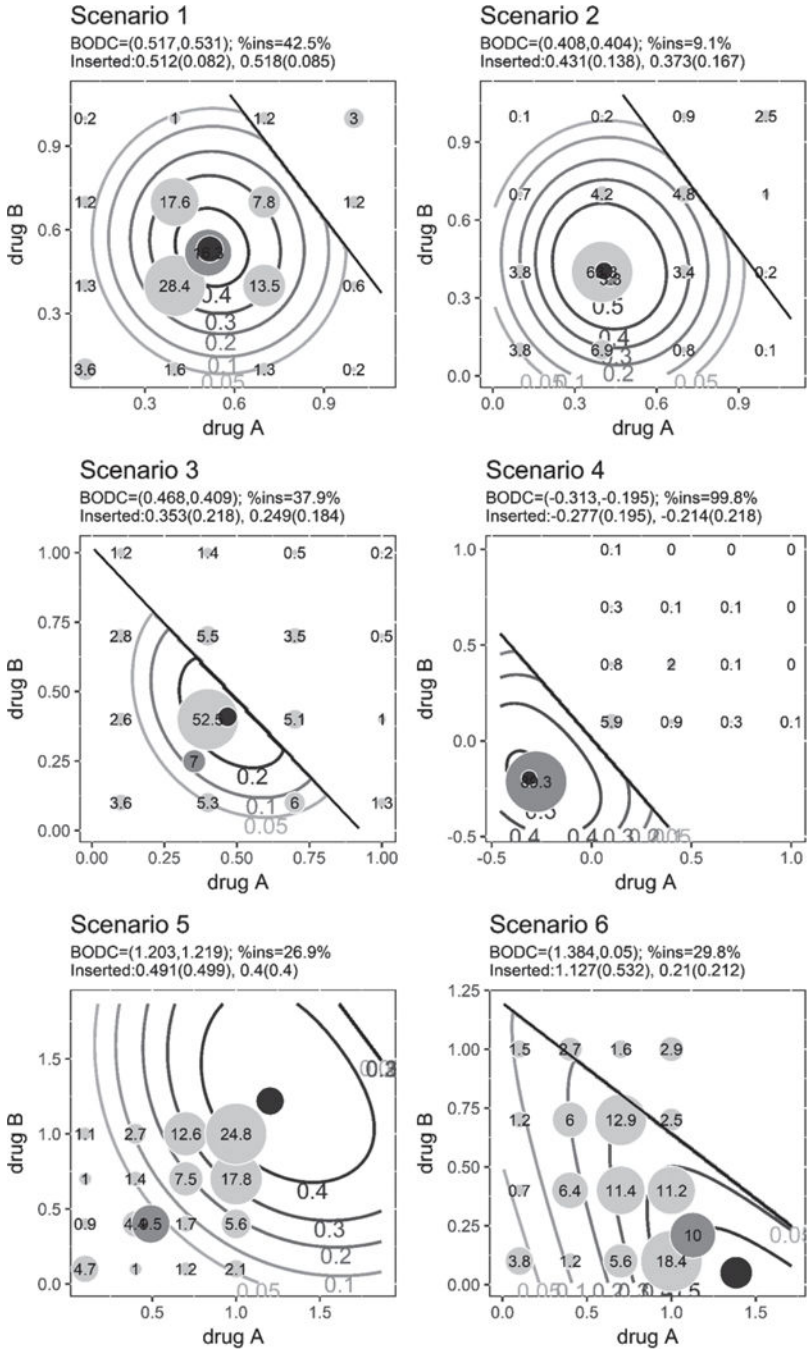

Fig. 4.

Galaxy plots of patients allocation for the AAA design (for each scenario are listed the true BODC, insertion rate and estimated inserted dose): ●, prespecified doses; ●, inserted dose (the size of and value inside each dot indicate the percentage of patients allocated to the dose combination); ●, true BODCs; ◡, dose–utility contour; ↘, toxicity pT-boundary (any dose combinations beyond the p_T-boundary with higher toxicity probability are of 0 utility)

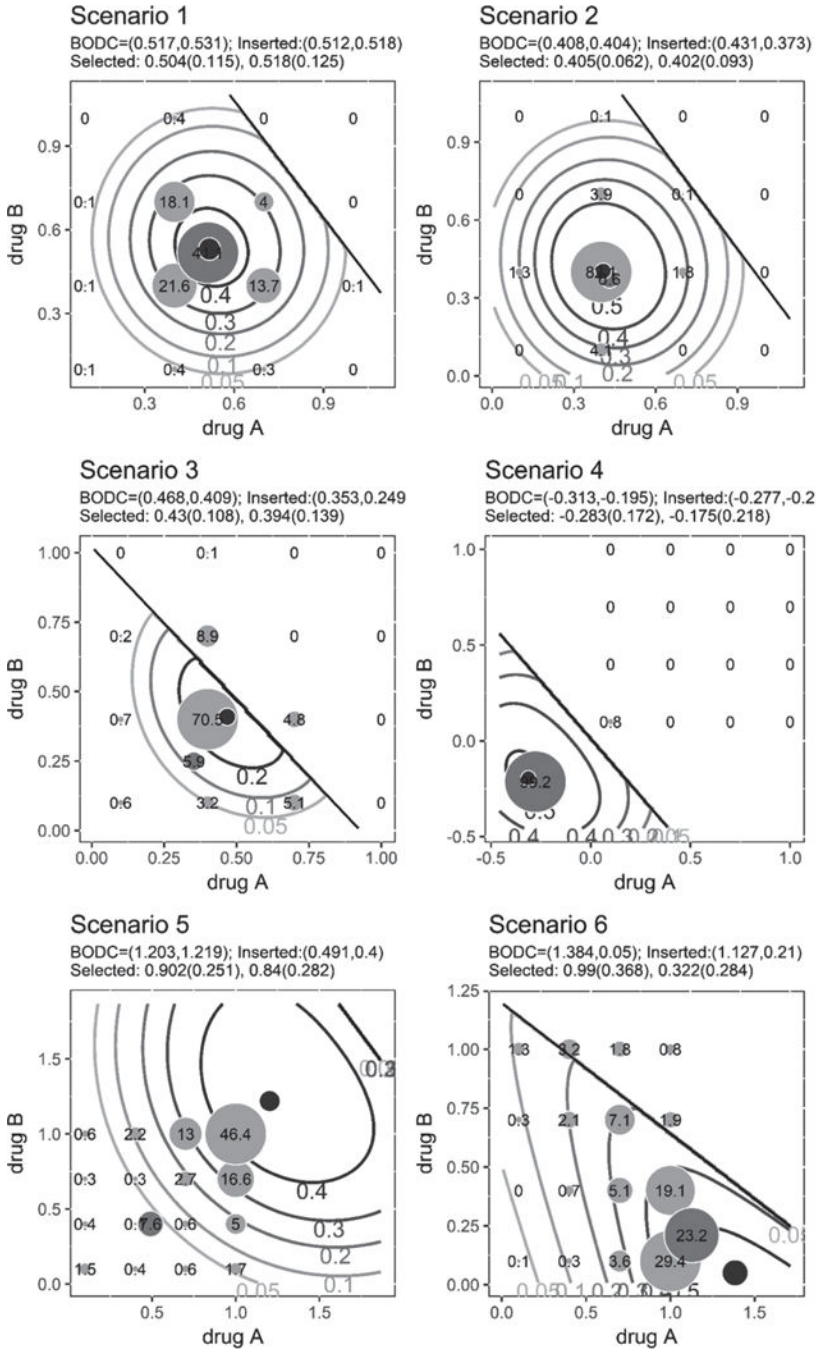

Fig. 5.

Galaxy plots of BODC recommendation for the AAA design (for each scenario are listed the true BODC, insertion rate and estimated inserted dose): ●, prespecified doses; ●, inserted dose (the size of and value inside each dot indicate the percentage of patients who were allocated to the dose combination); ●, true BODCs; ◡, dose–utility contour; ◥, toxicity p_T-boundary (any dose combinations beyond the p_T-boundary with higher toxicity probability are of 0 utility)

Table 1.

Median probability model selection rules

p_3	p_4	β_3	β_4	*Selected dose–efficacy model*
$< \frac{1}{2}$	$< \frac{1}{2}$	=0	=0	Linear logistic model, M_1
$\geqslant \frac{1}{2}$	$< \frac{1}{2}$	≠0	=0	Quadratic for agent A, M_2
$< \frac{1}{2}$	$\geqslant \frac{1}{2}$	=0	≠0	Quadratic for agent B, M_3
$\geqslant \frac{1}{2}$	$\geqslant \frac{1}{2}$	≠0	≠0	Quadratic for both agents A and B, M_4

Table 2.

AAA design for phase I–II dose finding trials

The trial starts with the treatment of the first cohort of patients at the lowest dose $(x_{a,1}, x_{b,1})$: suppose that patients are being treated at dose $\mathbf{x}_{jk} = (x_{a,j}, x_{b,k})$; a dose is deemed too toxic and unacceptable if $\Pr\{p(\mathbf{x}_{jk}) > p_T|\text{data}\} > \xi$, where ξ is close to 1; otherwise, the dose is acceptable; let N_1 and N denote the maximum sample size of stage I and the entire trial respectively

Stage I: run-in period

I1: on the basis of the observed data (y_{jk}, n_{jk}) at dose $\mathbf{x}_{jk}$, perform one of the three decisions, 'escalate to $\mathbf{x}_{j+1,k+1}$', 'stay at $\mathbf{x}_{jk}$ ' or 'de-escalate', according to design mTPI-2

I2: start stage II if either of the three conditions is satisfied:

(a) when the decision from I1 is 'de-escalate',

(b) when the decision from I1 is stay at $\mathbf{x}_{jk}$ and at least 9 patients have been assigned to this dose and

(c) when the highest dose combination $(x_{a,J}, x_{b,K})$ or the maximum sample size of stage I N_1 has been reached

Stage II: adaptive dose finding

Let $n_1 (\leqslant N_1)$ be the number of enrolled patients in stage I, $N_2 = N - n_1$ the maximum sample size for stage II and n_2 the number of patients currently enrolled in stage II

II1: once a cohort completes follow-up, collect efficacy and toxicity outcomes from all completers

II2: using the accumulated trial data, generate MCMC posterior samples of parameters under models M1, M2, M3 and M4, and carry out adaptive model selection: suppose that model l^* is selected; denote the MCMC posterior sample $\left\{\theta_{l^*}^{(b)}, b = 1, \ldots, B\right\}$ under the selected dose–efficacy model M_{l^*}, $l^* \in \{1, 2, 3, 4\}$

II3: obtain a posterior sample of $\mathbf{x}_{\text{opt}}$ under model M_{l^*}, i.e, $\left\{\hat{\mathbf{x}}_{\text{opt}, l^*}^{(b)}, b = 1, 2, \ldots, B\right\}$, from equation (9); then compute the posterior mean BODC $\hat{\mathbf{x}}_{\text{opt}} = (\hat{x}_{a,\text{opt}}, \hat{x}_{b,\text{opt}})$ from equation (10), and the decision indicator $\hat{A}$ in equation (10)

(a) If $\hat{A} = 1$, the new dose $\hat{\mathbf{x}}_{\text{opt}}$ is inserted in the trial and assigned to the next cohort: in addition, two sets of doses $\left\{(x_{a,1}, \hat{x}_{b,\text{opt}}), \ldots, (x_{a,J}, \hat{x}_{b,\text{opt}})\right\}$ and $\left\{(\hat{x}_{a,\text{opt}}, x_{b,1}), \ldots, (\hat{x}_{a,\text{opt}}, x_{b,K})\right\}$ are inserted as well; then go to II1 and wait for the completion of this cohort

(b) If $\hat{A}$, and $\mathbf{x}_{jk}$ is acceptable,

(i) identify $\mathcal{A}_1$ as the set of safe neighbours of $\mathbf{x}_{jk}$ with degree 1;

(ii) in $\mathcal{A}_1$, identify the dose $\mathbf{x}_{j^*k^*}$ that has the highest posterior mean utility under the safety constraint $J^* - j + k^* - k \leq 1$, from equation (11);

(iii) If $n_{j^*k^*} = 0$ or $n_{rs} \neq 0$, $\forall \mathbf{x}_{r,s} \in \mathcal{A}_1$, treat the next cohort at dose $\mathbf{x}_{j^*k^*}$; otherwise, if

$$\Pr\left\{U(\mathbf{x}_{j^*k^*}, \theta_{l^*}|\text{data}) > U_0\right\} > \left(\frac{N_2 - n_2}{N_2}\right)^{\omega},$$

treat the next cohort at $\mathbf{x}_{j^*k^*}$; otherwise, remove $\mathbf{x}_{j^*k^*}$ from $\mathcal{A}_1$ and go to step (b)(ii)

(c) If $\hat{A} = 0$ and $\mathbf{x}_{jk}$ is unacceptable, de-escalate to the untried 1-degree lower doses allowing cohort division:

(i) if $\{j,k \geqslant 2$ and $n_{j-1,k} = n_{j,k-1} = 0\}$, simultaneously enrol two cohorts of patients at both doses $\mathbf{x}_{j-1,k}$ and $\mathbf{x}_{j,k-1}$

(ii) if $\{j,k \geqslant 2$ and $n_{j-1,k} = 0$ but $n_{j,k-1} > 0\}$, or $\{ j \geqslant 2, k = 1$ and $n_{j-1,k} = 0 \}$, assign the next cohort to dose $\mathbf{x}_{j-1,k}$;

(iii) if $\{j,k \geqslant 2$ and $n_{j,k-1} = 0$ but $n_{j-1,k} > 0\}$, or $\{ k \geqslant 2, j = 1$ and $n_{j,k-1} = 0 \}$ assign the next cohort to dose $\mathbf{x}_{j,k-1}$;

(iv) otherwise, terminate this cohort and do not recommend any dose

(d) If no dose is recommended in (a)–(c), assign the next cohort to the dose $\mathbf{x}_{\tilde{j}\tilde{k}}$ which has the highest posterior mean utility among all the existing acceptable doses, i.e. $\mathbf{x}_{\tilde{j}\tilde{k}} = \text{argmax}_{\mathbf{x}_{j'k'}}\left\{\bar{U}(\mathbf{x}_{j'k'}, \theta_{l^*})\right\}$

II4: repeat II1–II3 until the maximum sample size N is reached

II5: select the dose that has the highest mean utility among all tested acceptable doses, including the newly inserted doses

Table 3.

Practical rules

Rule 1 (dose extrapolation): the inserted new dose is not allowed to be more than twice the highest dose or less than half of the lowest dose that has been used in the trial on the basis of the original scale of the dose level
Rule 2 (early termination): if the lowest dose $\mathbf{x}_{11} = (x_{a,1}, x_{b,1})$ is deemed unacceptable, i.e. $\Pr\{p(\mathbf{x}_{11}) > p\mathrm{T} \mid \text{data} > \xi$, where ξ is close to 1, and no new dose is inserted, terminate the trial
Rule 3 (dose exclusion): if the dose $\mathbf{x}_{jk} = (x_{a,j}, x_{b,k})$ is deemed unacceptable, i.e. $\Pr\{p(\mathbf{x}_{jk}) > p\mathrm{T} \mid \text{data} > \xi$, where ξ is close to 1, exclude doses $\left\{(x_{a,j'}, x_{b,k'}): j' = j, j+1, \ldots, J, k' = k, k+1, \ldots, K\right\}$, i.e. these doses will never be used in the trial again
Rule 4 (no skipping dose): restrict the escalation to a 1-level increment, i.e. there is no skipping in the escalation; particularly, if the new dose intended for insertion is higher than any unexplored dose, pause the insertion and go to steps II3(b)–II3(d) in Table 2

Table 4.

Simulation results for scenarios 1–6[†]

Scenario 1

1: quadratic; efficacy peaks on the left-hand side of MTD; insertion is needed

2: toxicity parameter estimation, true $(\alpha_0,\alpha_1,\alpha_2)$=(−1.6, 1.4, 1) $\hat{\alpha}_0 = -1.562(0.339)$ $\hat{\alpha}_1 = 1.227(0.99)$ $\hat{\alpha}_2 = 1.114(0.94)$

3: efficacy parameter estimation, true $(\beta_0, \beta_1, \beta_2, \beta_3, \beta_4)$=(1.3, 0.7, 0.7,−9.8,−8)

	$\hat{\beta}_0$	$\hat{\beta}_1$	$\hat{\beta}_2$	$\hat{\beta}_3$	$\hat{\beta}_4$
Linear	1.901 (0.808)	5.103 (2.673)	3.705 (1.663)	—	—
Quadratic of agent A	1.309 (0.529)	0.536 (1.644)	1.374 (1.384)	−22.987 (9.836)	—
Quadratic of agent B	1.245 (0.664)	2.049 (1.543)	0.665 (1.946)	—	−23.533 (11.582)
Quadratic of both agents	1.452 (0.531)	0.63 (1.602)	0.766 (1.545)	−14.335 (7.863)	−12.363 (6.861)

4: model selection percentages

Linear, 0.2%	Quadratic of agent A, 6.7%	Quadratic of both agent B, 5%	Quadratic of both agents, 88.1%

5: true toxicity and efficacy probability and utility (Tox/Eff/Ut)

Dose level (B\A)	0.1	0.4	0.7	1
1	0.14/0.01/0	0.22/0.18/0.06	0.32/0.23/0	0.45/0.02/0
0.7	0.1/0.07/0.03	0.16/0.65/0.34	0.24/0.71/0.29	0.36/0.15/0
0.4	0.07/0.05/0.02	0.11/0.59/0.34	0.18/0.65/0.32	0.27/0.12/0.03
0.1	0.05/0/0	0.08/0.09/0.04	0.13/0.12/0.05	0.2/0.01/0

6: trial safety

	Early termination (%)	DLT rate	Trials with DLT rate > 0.3 (%)
AAA design	0	0.168 (0.038)	0
Cai's design	0	0.161 (0.036)	0

Scenario 2

1: quadratic; efficacy peaks on the left-hand side of MTD; insertion is not needed

2: toxicity parameter estimation, true $(\alpha_0,\alpha_1,\alpha_2)$=(−1.6, 1.4, 1) $\hat{\alpha}_0 = -1.391(0.364)$ $\hat{\alpha}_1 = 1.264(1.054)$ $\hat{\alpha}_2 = 1.093(0.955)$

3: efficacy parameter estimation, true $(\beta_0, \beta_1, \beta_2, \beta_3, \beta_4)$=(1.5,−1.7,−1.5,−9,−7)

	$\hat{\beta}_0$	$\hat{\beta}_1$	$\hat{\beta}_2$	$\hat{\beta}_3$	$\hat{\beta}_4$

Linear	—	—	—	—	—
Quadratic of agent A	1.899 (0.647)	−2.155 (2.16)	1.491 (1.574)	−19.774 (8.165)	—
Quadratic of agent B	1.76 (0.728)	1.515 (1.723)	−2.727 (2.076)	—	−22.577 (9.173)
Quadratic of both agents	1.931 (0.571)	−1.113 (1.936)	−1.182 (1.848)	−12.913 (6.594)	−10.528 (5.093)

4: model selection percentages

Linear, 0%	Quadratic of agent A, 9.8%	Quadratic of agent B, 5.2%	Quadratic of both agents, 85%

5: true toxicity and efficacy probability and utility (Tox/Eff/Ut)

Dose level (B\A)	0.1	0.4	0.7	1
1	0.16/0.02/0.01	0.25/0.15/0.04	0.37/0.08/0	0.5/0/0
0.7	0.12/0.25/0.11	0.19/0.72/0.36	0.28/0.57/0.18	0.4/0.04/0
0.4	0.08/0.37/0.2	0.13/0.82/0.52	0.21/0.7/0.32	0.31/0.08/0
0.1	0.06/0.11/0.05	0.1/0.5/0.28	0.15/0.34/0.15	0.24/0.02/0

6: trial safety

	Early termination (%)	DLT rate	Trials with DLT rate > 0.3 (%)
AAA design	0	0.159 (0.036)	0.1
Cai's design	0	0.156 (0.036)	0

Scenario 3

1: quadratic; efficacy peaks on the right-hand side of MTD; only a few dose combinations are tolerable; insertion is needed

2: toxicity parameter estimation, true $(\alpha_0,\alpha_1,\alpha_2)=(-0.5, 2.2, 2)$ $\hat{\alpha}_0 = -0.569(0.365)$ $\hat{\alpha}_1 = 1.694(1.078)$ $\hat{\alpha}_2 = 1.583(0.991)$

3: efficacy parameter estimation, true $(\beta_0, \beta_1, \beta_2, \beta_3, \beta_4)=(1.6, 2, 0.9,-8.5,-7)$

	$\hat{\beta}_0$	$\hat{\beta}_1$	$\hat{\beta}_2$	$\hat{\beta}_3$	$\hat{\beta}_4$
Linear	—	—	—	—	—
Quadratic of agent A	1.922 (0.717)	1.125 (1.761)	3.521 (1.559)	−21.879 (10.383)	—
Quadratic of agent B	1.965 (0.742)	4.68 (2.091)	0.554 (1.67)	—	−18.42 (8.554)
Quadratic of both agents	1.743 (0.658)	1.455 (1.705)	1.253 (1.525)	−14.95 (7.333)	−7.525 (4.776)

4: model selection percentages

Linear, 0%	Quadratic of agent A, 13.4%	Quadratic of agent B, 8.9%	Quadratic of both agents, 77.7%

5: true toxicity and efficacy probability and utility (Tox/Eff/Ut)

Dose level (B\A)	0.1	0.4	0.7	1

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1	0.35/0.01/0	0.56/0.28/0	0.75/0.46/0	0.87/0.12/0
0.7	0.2/0.07/0.02	0.37/0.69/0	0.58/0.83/0	0.76/0.45/0
0.4	0.1/0.05/0.02	0.21/0.61/0.26	0.39/0.77/0	0.6/0.37/0
0.1	0.05/0/0	0.11/0.12/0.05	0.23/0.23/0.07	0.41/0.05/0

6: trial safety

	Early termination (%)	DLT rate	Trials with DLT rate> 0.3 (%)
AAA design	0	0.253 (0.045)	16.4
Cai's design	0	0.254 (0.041)	13.4

Scenario 4

1: quadratic; efficacy peaks on the right-hand side of MTD; all doses are overly toxic; insertion is needed

2: toxicity parameter estimation, true (α_0,α_1,α_2)=.0.7, 1.2, 1) $\hat{\alpha}_0 = 0.537(0.999)$ $\hat{\alpha}_1 = 1.039(0.764)$ $\hat{\alpha}_2 = 0.979(0.774)$

3: efficacy parameter estimation, true (β_0, β_1, β_2, β_3, β_4)=(−2,−6.6,−5,−4,−3.6)

	$\hat{\beta}_0$	$\hat{\beta}_1$	$\hat{\beta}_2$	$\hat{\beta}_3$	$\hat{\beta}_4$
Linear	2.576 (1.801)	0.112 (1.456)	0.851 (1.471)	—	—
Quadratic of agent A	1.812 (1.901)	−4.768 (2.539)	0.809 (1.39)	−3.955 (1.69)	—
Quadratic of agent B	1.532 (1.737)	−0.247 (1.206)	−3.363 (2.355)	—	−3.513 (1.567)
Quadratic of both agents	0.398 (1.669)	−4.348 (2.389)	−3.591 (2.382)	−3.071 (1.471)	−3.388 (1.53)

4: model selection percentages

Linear, 17.9%	Quadratic of agent A, 24%	Quadratic of agent B, 28.9%	Quadratic of both agents, 28.9%

5: true toxicity and efficacy probability and utility (Tox/Eff/Ut)

Dose level (B\A)	0.1	0.4	0.7	1
1	0.64/0.03/0	0.74/0.01/0	0.82/0/0	0.88/0/0
0.7	0.55/0.35/0	0.66/0.12/0	0.76/0.01/0	0.83/0/0
0.4	0.45/0.79/0	0.57/0.49/0	0.68/0.07/0	0.77/0/0
0.1	0.36/0.9/0	0.47/0.69/0	0.59/0.15/0	0.69/0/0

6: trial safety

	Early termination (%)	DLT rate	Trials with DLT rate > 0.3 (%)
AAA design	2.6	0.215 (0.057)	7.2
Cai's design	51.3	0.509 (0.151)	99.5

Scenario 5

1: quadratic; all doses are safe; the dose range covers only the bottom left-hand corner of the efficacy–dose curve; insertion is needed

2: toxicity parameter estimation, true $(\alpha_0,\alpha_1,\alpha_2)$=(−1.6, 0.3, 0.2) $\hat{\alpha}_0 = -1.842(0.492)$ $\hat{\alpha}_1 = 0.788(0.723)$ $\hat{\alpha}_2 = 0.709(0.672)$

3: efficacy parameter estimation, true $(\beta_0, \beta_1, \beta_2, \beta_3, \beta_4)$=(−1.45, 3.8, 2.8,−1.3,−1)

	$\hat{\beta}_0$	$\hat{\beta}_1$	$\hat{\beta}_2$	$\hat{\beta}_3$	$\hat{\beta}_4$
Linear	−2.083 (0.991)	3.237 (1.548)	2.298 (1.408)	—	—
Quadratic of agent A	−2.775 (1.404)	4.051 (2.239)	2.251 (1.469)	−1.668 (3.157)	—
Quadratic of agent B	−2.351 (1.206)	3.248 (1.643)	3.44 (2.32)	—	−3.307 (3.509)
Quadratic of both agents	−3.055 (1.64)	4.095 (2.481)	3.157 (2.238)	−2.22 (3.657)	−3.124 (3.658)

4: model selection percentages

Linear, 25.7% Quadratic of agent A, 24.8% Quadratic of agent B, 23.9% Quadratic of both agents, 25.6%

5: true toxicity and efficacy probability and utility (Tox/Eff/Ut)

Dose level (B\A)	0.1	0.4	0.7	1
1	0.16/0.06/0.02	0.18/0.28/0.11	0.19/0.63/0.29	0.21/0.83/0.42
0.7	0.15/0.03/0.01	0.17/0.15/0.05	0.18/0.44/0.18	0.2/0.69/0.33
0.4	0.14/0.01/0	0.15/0.06/0.02	0.17/0.21/0.08	0.19/0.44/0.18
0.1	0.13/0/0	0.15/0.01/0.01	0.16/0.06/0.02	0.18/0.16/0.06

6: trial safety

	Early termination (%)	DLT rate	Trials with DLT rate > 0.3 (%)
AAA design	0.4	0.196 (0.057)	0.3
Cai's design	0.3	0.195 (0.057)	0.4

Scenario 6

1: linear; insertion is needed

2: toxicity parameter estimation, true $(\alpha_0,\alpha_1,\alpha_2)$=(−1.46, 0.77, 1.39) $\hat{\alpha}_0 = -1.424(0.422)$ $\hat{\alpha}_1 = 0.934(0.781)$ $\hat{\alpha}_2 = 1.272(0.868)$

3: efficacy parameter estimation, true $(\beta_0, \beta_1, \beta_2, \beta_3, \beta_4)$=(0.3, 3.1, 1.55,—,—)

	$\hat{\beta}_0$	$\hat{\beta}_1$	$\hat{\beta}_2$	$\hat{\beta}_3$	$\hat{\beta}_4$
Linear	0.187 (0.453)	3.142 (1.071)	1.521 (1.082)	—	—
Quadratic of agent A	0.324 (0.609)	5.394 (2.16)	1.85 (1.256)	−9.503 (3.96)	—

Quadratic of agent B	0.482 (0.58)	3.711 (1.287)	1.148 (1.766)	—	−9.184 (3.549)
Quadratic of both agents	0.287 (0.845)	5.883 (2.48)	1.867 (2.135)	−11.798 (5.545)	−9.536 (4.105)

4: model selection percentages

Linear, 62%	Quadratic of agent A, 16%	Quadratic of agent B, 17.5%	Quadratic of both agents, 4.5%

5: true toxicity and efficacy probability and utility (Tox/Eff/Ut)

Dose level (B\A)	0.1	0.4	0.7	1
1	0.25/0.35/0.11	0.31/0.65/0	0.38/0.86/0	0.45/0.95/0
0.7	0.16/0.23/0.09	0.21/0.5/0.2	0.26/0.77/0.31	0.32/0.92/0
0.4	0.1/0.14/0.06	0.13/0.35/0.16	0.17/0.65/0.32	0.22/0.86/0.43
0.1	0.06/0.08/0.04	0.08/0.23/0.11	0.11/0.5/0.27	0.14/0.77/0.46

6: trial safety

	Early termination (%)	DLT rate	Trials with DLT rate > 0.3 (%)
AAA design	0.1	0.202 (0.049)	1.3
Cai's design	0	0.201 (0.041)	1

† For each scenario, 1000 trials are conducted by computer and the operating characteristics are summarized in six sections. Section 1 gives a brief description of the true dose response and the need for insertion or not. Sections 2 and 3 provide the average (standard deviation) of the posterior means across 1000 simulated trials for the regression parameters. Section 4 summarizes the model selection. Section 5 presents the true toxicity and efficacy probability and utility at each dose combination and Section 6 presents the trial safety in terms of early termination frequency, overall DLT rate and percentage of trials with DLT rate greater than p_T =0.3 for both the AAA design and the design in Cai *et al.* (2014).

Table 5.

Time duration comparison between the ACD algorithm and the single cohort under AAA[†]

Scenario	Algorithm	Mean (days)	Minimum ~ maximum (days)	p-value
1	Cohort expansion	993.2 (161.9)	35 ~ 1078	0:0687
	Single cohort	1030.54 (102.4)	35 ~ 1078	
2	Cohort expansion	986.01 (172.01)	35 ~ 1074	0:0126[‡]
	Single cohort	1029.43 (110.76)	35 ~ 1076	
3	Cohort expansion	935.1 (201.36)	35 ~ 1075	<0:0001[§]
	Single cohort	1023.29 (108.68)	35 ~ 1072	
4	Cohort expansion	741.75 (448.36)	34 ~ 1077	0.6843
	Single cohort	749.91 (448.76)	34 ~ 1071	
5	Cohort expansion	984.25 (221.82)	13 ~ 1075	0.4032
	Single cohort	992.41 (214.45)	13 ~ 1083	
6	Cohort expansion	979.98 (178.49)	28 ~ 1073	0:0021[‡]
	Single cohort	1022.02 (129.18)	28 ~ 1078	
7	Cohort expansion	1001.89 (159.84)	35 ~ 1079	0:0714
	Single cohort	1044.55 (91.66)	35 ~ 1083	
8	Cohort expansion	1027.4 (100.73)	36 ~ 1075	0.4143
	Single cohort	1035.1 (79.58)	35 ~ 1078	
9	Cohort expansion	1024.49 (104.33)	35 ~ 1076	0.3268
	Single cohort	1036.92 (75.89)	35 ~ 1078	
10	Cohort expansion	988.3 (168.62)	35 ~ 1075	<0:0113[‡]
	Single cohort	1028.7 (110.98)	35 ~ 1078	
11	Cohort expansion	997.2 (166.25)	24 ~ 1072	0:2232
	Single cohort	1023.39 (134.85)	24 ~ 1084	

[†]Entries are the simulated trial duration in days for two-agent trials with a sample size of 96 patients.

[‡]p-value < 0.05.

[§]p-value < 0.0001.