Monotonic Dose Response And Curve-Free Designs for Phase I Dose-Finding Trials

Shenghuan Fan, Bee Leng Lee, Ying Lu, and Jiapeng Xu

Abstract Traditionally, a dose-toxicity curve is assumed to be monotonic, with the ultimate goal of finding the maximum tolerated dose (MTD). Whereas model-based designs typically use parametric models to facilitate the exchange of information across dose levels, curve-free designs rely solely on the monotonic assumption to extrapolate data between doses. In first part of this chapter, we present several curve-free designs for phase I trials that were developed over the past decade to identify the MTD in trials involving one or two agents. In recent years, the search for biologically efficacious doses (BEDs) has become increasingly intriguing. Researchers are seeking the optimal efficacy among tolerated doses. The second part of this chapter presents a curve-free design and a hybrid design for BED-finding trials involving two agents, assuming a monotonic dose-toxicity curve and a unimodal dose-efficacy curve. The last section of the chapter provides examples and demonstrations of our web-based R packages.

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1 Introduction

”A good beginning is half the battle.” Phase I trial is the first in human test for new drugs. The objectives are to test the drug safety, establish the side effect profiles, and define the acceptable dose, dose schedule, and method of administration for the subsequent drug development processes. In oncology drug development, because of anticipated side effects of cancer drugs, phase I trials have been traditionally conducted based on a small number of cancer patients, often with multiple types of relevant cancers, and have been previously failed by standard cares. Therefore, investigators not only concern about safety, i.e., avoid unnecessary harms to patients, but also wish to find effective amount of drug leading to outcome improvement.

For many years, cancer treatment efficacy is correlated to the cytotoxicity of chemotherapy drugs. As a result, the focus of patient I trial is to increase the dose to the maximum tolerated level. Pre-defined dose limiting toxicity (DLT) events are defined in the protocol. The proportion of patients who are tested at a given dose and experience of any DLT events in the first cycle of chemotherapies is defined as DLT rate. Under an assumption that DLT rate increases with the dose, a maximum tolerated dose (MTD) is the highest dose that results in the toxicity rate under acceptable level, traditionally in the range close to 30%. For chemotherapy, the MTD is also expected to deliver the best treatment benefits to patients.

Most traditional phase I trial designs have been focused on identification of MTDs in an efficient way that uses the least number of patients, with more patients near MTDs, less patients exposed above MTDs, and higher probability to recommend correct MTDs. Since the sample size is so small, no formal statistical inference is possible. The designs are either based on empirical argument, such as rule based 3+3 design [1], or model-based approach, such as continuous reassessment methods[2], to guide the decision to increase or decrease the dose levels for the next cohort of patients.

With the emergent of novel cancer treatments, such as molecular targeted therapies, immunotherapies, and cell therapies, the DLT rates have been much less than the traditional cytotoxicity agents[3]. In addition, the efficacy may not necessarily increase beyond certain dose levels. As a result, novel phase I designs have been proposed in the past 2 decades. Most popular designs are Bayesian optimal interval design (BOIN)[4], mTPI2 design[5], etc., which are explicit and flexible in the selection of the MTD goal, higher probability to place patients at MTD, and higher probability to recommend MTD at the end of trial. The acceptance of these methods not only due to their performance, but also the tremendous efforts of statisticians to create statistical software packages, such as trialdesigns.org, to facilitate their implementations.

Curve-free dose finding design is a group of non-parametric designs that use a monotonic toxicity dose response assumption only. It may or may not use Bayesian argument. These design methods have been developed and published in literature[8, 10, 11, 13, 14] without software available. As a result, they have not yet widely used in phase I trials. In this chapter, we present these designs in a systematic approach. Section 2 focuses on finding MTD of a single agent. Section 3 presents three designs

for MTDs of two-agents. Section 4 changes the topic from MTD to the biological efficacious doses in single agent trials and provided two designs. Section 5 presents the first time, an R-package and Web-based Shiny app for all these designs, for trial implementations. While the most contents of Sections 2 to 4 have been previously published, we made effort to simplify the explanations and added some new results.

2 Maximum Tolerated Dose in One-Agent Trials

In recent decades, the poor operating characteristics of the traditional 3+3 design have prompted the development of more sophisticated alternatives, notably model based designs, which assume a parametric dose-toxicity relationship to estimate the maximum tolerated dose (MTD). Despite the demonstrated superior operating characteristics of model-based designs, their adoption in clinical trials remains limited, primarily due to the intricacies of statistical modeling and demanding computational requirements. In response to these challenges, we introduced curve-free alternatives that are relatively easy for clinicians to understand and implement. Curve-free methods are so called because they require no explicit modeling of the dose-toxicity curve. Instead, they rely on the classical assumption that the relationship between dose and toxicity is nondecreasing, which are particularly applicable to cytotoxic drugs.

In the first two sections, we introduce curve-free algorithms for finding the maximum tolerated dose (MTD), which is defined as the $\theta_{\mathrm{T}}-$percentile of the dose-DLT curve. We will begin with the simplest situation, one agent and one DLT outcome, to a more complicated situation, two agent and one or two DLT outcome(s).

2.1 Working Model

We assume the dose-DLT relationship being monotonic or say non-decreasing. This is the only assumption about the shape of the relationship.

Let T_i be a patient's response at dose x_i: 1 means DLT is present and 0 means absent; $\{x_1 < x_2 < ... < x_k\}$ be the dose domain of study; and p_i be the DLT probability at x_i: $p_i = P(T_i = 1)$. Therefore, T_i follows $\mathrm{Ber}(p_i)$, a Bernoulli distribution with success probability p_i. We add the conjugate beta distribution $\mathrm{Beta}(a_i, b_i)$ on the parameter p_i as the prior distribution. After treating a patient at dose x_i, the updated prior (or posterior) distribution of p_i given his/her response $T_i = t_i$ is then $\mathrm{Beta}(a_i + t_i, b_i + 1 - t_i)$. One obvious advantage of this (working) model is the existence of analytic forms of posterior probabilities.

Throughout, the superscript 0 attached to a parameter will denote its initial value. The initial Beta parameters a_i^0, b_i^0 must be chosen to hold the monotonic property on the mean DLT probability at x_i: $\mu_1^0 \le \mu_2^0 \le ... \le \mu_k^0$ where $\mu_i^0 = \frac{a_i^0}{a_i^0+b_i^0}$. The selection of parameters a_i^0, b_i^0 is critical for the efficiency of the design, especially

for small samples. We suggest to have investigators provide the estimate of p_i at each dose and make sure they follow the monotonic property. These estimates will serve as μ_i^0 and the initial prior parameters (a_i^0, b_i^0) are set as follows:

$$a_i^0 = c\mu_i^0 > 0$$
$$b_i^0 = c(1 - \mu_i^0) > 0$$

where c is a positive constant presenting the informative level of the prior distribution. Note that c can be treated as the "equivalent" sample size of the prior distribution. For example, if $c = 2$ and the initial estimates μ_i are mis-specified, then it will take two or more patients to fix the error. General speaking, if less informative priors are desired, indicating less confidence in the preliminary estimate of p_i and/or a strong preference for a data-driven strategy, then the constant c should be set as small. However, as we wish the shapes of the Beta priors near the MTD being unimodal, the c value is suggested to be large enough so that the parameters a, b at (or near) the true MTD (with DLT probability of θ_T) are both greater than one:

$$a = c\mu = c\theta_T > 1$$
$$b = c(1 - \mu) = c(1 - \theta_T) > 1.$$

For example, we can use $c = 4$ for target probability $\theta_T = .33$, and $c = 6$ for target probability $\theta_T = .20$. Another advantage of Beta distributions is the variety of distribution shapes. By setting parameters a, b in this way, the prior distributions at doses near MTD would be unimodel; at doses lower than MTD ($a < b$) would be increasing; and at doses higher than MTD ($a > b$) would be decreasing as wished.

Although the monotonic DLT curve is assumed, the isotonic method is not recommend as it tends to flat a curve. An example will explain this point. Suppose that there are three doses x_1, x_2, x_3 of study and a cohort of three patients are assigned to each dose. If one DLT is observed at each dose of x_1, x_2 but zero DLT at the highest dose x_3, the monotonic property is obviously violated because the sample proportion at x_3 (0/3) is lower than that at x_1 (1/3). Therefore, the isotonic regression method will pool the three cohorts together to maintain the monotonic property and the isotonic estimates (pooled sample proportions) at all doses become the same as $(1 + 1 + 0)/(3 + 3 + 3) = 2/9$ as shown in Table 1.

Table 1 the observed, isotonic (pooled) and working frequencies

Type	No. of	x_1	x_2	x_3
observed:	DLTs	1	1	0
	patients	3	3	3
pooled:	DLTs	2	2	2
	patients	9	9	9
working:	DLTs	1	2	2
	patients	8	7	5

The isotonic regression method is consistent if the monotonic property truly holds and thus it could be a good in estimation. However, it could suffer the overshooting problem in identifying MTD. In the above example, suppose the target DLT probability is .30 and then based on the sample proportion, even the lowest dose x_1 (1/3) is not acceptable. But after adjusted for monotonic property, the pooled sample proportions suggest all doses are acceptable and so x_3 will be recommended as MTD. Many investigators will consider the recommendation of x_3 in this case as overshooting. Due to the small sample size at each dose, it is quite possible to observe much lower number of DLTs than the expected at the higher doses.

To overcome the overshooting problem, we propose another way to extract information from the data. According to the monotonic property in a DLT curve, patients who can tolerate higher doses are expected to also tolerate lower doses, and patients who cannot tolerate lower doses are expected to experience DLTs at higher doses as well. With that said, even though each patient was treated at only one dose, their responses for some other doses could be predicted, called working DLT responses, as shown in Table 2. The "working" number of DLTs at a dose is the total number of patients with DLTs at this and lower doses. On the other hand, the "working" number of patients at a dose is the sum of all patients at this dose, those with DLTs at the lower doses, and those without DLTs at higher doses. For example as shown in Table 1, the working sample size at x_1 is sum of the number of patients at x_1, the number of patients without DLTs at x_2 and at x_3, which is $3 + 2 + 3 = 8$, while the working number of DLTs at x_1 is still 1. As shown in Table 1, based on the working data, x_3 will not be selected as MTD because the working sample proportion $2/5 = .40$ exceeds the target DLT probability .30 and so the working data somehow drags the recommended MTD back as wished here.

Table 2 working DLT responses and working posteriors Beta(a, b) at different doses

Observed T_i		x_1	x_2	...	x_i	x_{i+1}	...	x_k
1:	working DLT	–	–	–	1	1	1	1
	beta parameter a	a_1	a_2	...	$a_i + 1$	$a_{i+1} + 1$	...	$a_k + 1$
	beta parameter b	b_1	b_2	...	b_i	b_{i+1}	...	b_k
0:	working DLT	0	0	0	0	–	–	–
	beta parameter a	a_1	a_2	...	a_i	a_{i+1}	...	a_k
	beta parameter b	$b_1 + 1$	$b_2 + 1$	...	$b_i + 1$	b_{i+1}	...	b_k

After extending the data in this way, the prior distribution Beta(a, b) of DLT probability is updated accordingly as shown in Table 2. It can be easily proved that the monotonic property is preserved on the posterior means. Because of the missing cells at the lower doses (when DLT is present) and at the higher doses (when DLT is absent), the DLT probabilities are underestimated at lower doses and overestimated at higher doses. This property prevents aggressive jump into higher doses. Therefore, instead of being a problem, the bias of the working estimation

actually helps overcome the overshooting tendency of Bayesian adaptive dose-finding designs [6].

2.2 Utility Function and Dose Selection Rule

We will construct an utility function according to the trial goals. An utility function consists of an individual gain function and a weight distribution over all applicable individuals. The choices of gain function and weight distribution should depend on the goal of a trial.

If the primary goal is to assign each patient, in-trial or future, to a dose as closely as possible to the MTD (the θ_T-percentile), a proper gain function of a dose assignment could be $-|p - \theta_T|$, where p is the DLT probability at this dose. The gain of zero means assigning a patient at MTD. The choice of weight distribution depends on how the benefits for in-trial and future patients are balanced. If the goal is to maximize the gains of future patients regardless of the gains of in-trial patients, the weight distribution puts mass one on future patients and zero on in-trial patients. Otherwise, the weight for in-trial patients could be w and that for future patients would be $1 - w$.

After the (individual) gain function and weight distribution are determined, the utility function is then TG, the total weighted gain from all in-trial and future patients. Let G_i denote the gain from patient i and n be the number of patients in the trial. The utility function TG can be expressed as $TG = w \sum_{i=1}^{n} G_i + (1 - w)G_{n+1}$.

The optimal dose assignment for a current patient i is the dose maximizing the expected utility function given the data, denoted by $\mathrm{E}(TG|\mathrm{Data}_i)$, where Data_i represents all the data collected up to (excluding) patient i. However, finding the optimal dose assignment is computationally infeasible for most situations [7]. Instead, the most myopic suboptimal strategy OSLA is mostly adopted in practice: OSLA pretends the current patient is the last one available. Therefore, for any positive weight w, OSLA always selects the best-so-far dose, which maximizes $\mathrm{E}(G_i|\mathrm{Data}_i)$, for the current patient; it is intuitively preferred.

2.3 Guideline of the CBA Design

The proposed curve-free Bayesian dose-finding design consists of six components: working model, starting cohort, utility function, dose selection rule and restrictions, sample size range, and stopping rule. Here are the guidelines for setting the six components:

1. Working model: Adopt the proposed isotonic regression model with Beta priors
2. Starting cohort for Bayesian methods: Assign a cohort to the lowest dose and escalate the dose until the first toxicity occurs, as suggested in [7]; the Bayesian algorithm is then adopted afterward for dose allocation.

3. Utility function: Choose the proper gain function, G, and the weight for in-trial patients, w; the utility function is the weighted total gain.
4. Dose selection rule and restrictions: Use either OSLA or another suboptimal strategy; OSLA is well studied and recommended. When necessary, include restrictions, such as limiting de-/escalation to one dose level.
5. Range for sample size n: Do not stop the trial before $n = n_{min}$ but it must stop at $n = n_{max}$. Because the priors could be set incorrectly at the beginning, the recommendations from the early cohorts could be misled by the mis-specified priors. Therefore, setting a minimal sample size is suggested.
6. Stopping rule: Before reaching the maximal sample size n_{max}, the trial will stop early if 1) the current recommended dose is very likely to be the MTD; that is, the next higher dose is very likely to be too toxic: $P[p_{MT\hat{D}^+} > u + \delta|data] > r_1$ where MTD^+ is the next higher dose from the current recommended dose, or 2) all doses are evidently too toxic: $P[p_1 > u + \delta|data] > r_2$. The percentages δ, r_1, r_2 are pre-selected as needed.

This design was published [8] and will be referred to as **c**urve-free **B**ayesian **a**daptive (CBA) design in the later sections. We defer the examples in Section 5.

3 Maximum Tolerated Dose in Two-Agent Trials

Combination trials, which involve the administration of two or more therapeutic agents, pose significantly greater challenges compared to single-agent trials. First of all, the ordering of the dose combinations in terms of DLT probabilities cannot be fully predetermined even in the case of two agents. For example, consider a two-agent trial in which agent A has I dose levels and agent B has J dose levels. Let (i, j), denote the combination of the ith dose level of agent A and the jth dose level of agent B. Without additional information, the combinations (1, 2) and (2, 1) do not have a clear ordering in terms of toxicity. Second, as the number of dose levels of one or more agents increases, the number of dose combinations increases rapidly. Consequently, more sophisticated and efficient designs are required for combination trials.

In this section, we present three curve-free designs for two-agent trials: two are rule-based, and the third is model-assisted.Specifying a predetermined search path may overlook one or more acceptable dose combinations. Therefore, our rule-based designs refrain from predefining any search path, allowing the data to dictate the direction of the search. Furthermore, only the natural partial ordering of the dose combinations are used to guide dose escalations and de-escalations. Let p_{ij} denote the DLT probability of a patient treated at dose combination (i, j). We assume throughout that $p_{ij} < p_{rs}$ whenever $i < r$ and $j \leq s$ or $i \leq r$ and $j < s$, and we denote this partial ordering of dose combinations by $(i, j) \prec (r, s)$.

3.1 A Rule-Based Design for Agents with Same Dose-Limiting Toxicities

The traditional 3+3 design is popular for determining the acceptance of a combination, despite its inefficiency. To address this, we develop a more efficient 2+1+3 design as a replacement.

3.1.1 Data-Driven 2+1+3 Design

In the standard 3+3 design, three patients are assigned to a given dose to determine if the dose is acceptable (no patient developed a DLT), potentially acceptable (one patient developed a DLT), or unacceptable (at least two patients developed DLTs). This can be considered an **exploration stage** to determine the safety of the given dose. If the dose is potentially acceptable, then three more patients are assigned the same dose to decide if the MTD has been exceeded (at least one patient developed a DLT). This can be considered a **confirmation stage**, the goal of which is to confirm that the dose is indeed acceptable. If the current dose is acceptable, it will be escalated; otherwise, it will be deescalated. A more aggressive algorithm is required in combination trials because a relatively large number of dose combinations are studied. Our first modification of the 3+3 design to improve efficiency is as follows.

Stage 1: exploration stage.

We adopt a 2+1 design to rapidly search for potentially acceptable dose combinations. For a given dose combination, a cohort of two patients is enrolled first. If neither patient developed a DLT, the dose combination is retained as a potentially acceptable combinations. In the event that both patients developed DLTs, the dose combination is rejected (unacceptable). Otherwise, a second cohort comprising one patient is enrolled for confirmation. Should this patient experience a DLT, the dose combination is rejected; otherwise it is retained for the next stage. Note that if a dose combination, say (i, j), is rejected, then all dose combinations of a higher (partial) order, $\{(r, s)|(i, j) \prec (r, s)\}$, are also rejected. We will defer the rules of dose de/escalation to a later point to ensure a smoother flow of ideas.

At the end of Stage 1, if no dose combination is retained, the trial is stopped and no MTD is concluded. Otherwise, the trial progresses to Stage 2.

Stage 2: confirmation stage.

First, the DLT probabilities of all tested and retained dose combinations are estimated, denoted as $\hat{p}_{ij}$, using *all* the available data. Two-dimensional isotonic estimates [9] are adopted here. Dose combinations with estimated DLT probabilities falling into a pre-specified interval are considered MTD candidates, and a cohort of three (or four

if only 2 patients were enrolled at Stage 1) patients is assigned to each candidate for confirmation. All the data accrued are used to update the DLT probabilities of all combinations and so the list of MTD candidate(s). Finally, the MTD candidate(s) with the highest partial order is(are) recommended as the MTD(s). If there is no MTD candidate, then no MTD is recommended.

3.1.2 Rules of Dose De/escalation in Stage 1

The primary principle of our dose de/escalation is to de/increase one dose of one agent at a time, leading to three possible decisions: de/increase one dose of agent 1, de/increase one dose of agent 2, or de/increase one dose for both agents. If the current combination (i, j) is retained and we decide to escalate, the next testing combination(s) could be either $(i + 1, j)$, or $(i, j + 1)$, or both. On the other hand, if (i, j) is rejected and we have to deescalate, the next testing combination(s) could be either $(i-1, j)$, or $(i, j-1)$, or both. Therefore, there are two types of our next testing combination(s): moving up/down in one agent (1-dimensional search, Figure 1) or moving up/down in both agents (2-dimensional search, Figure 2).

The following notations are defined for convenience. Let B be the set of dose combinations which were tested and R be the set of combinations which were rejected. In addition, let $N^+(i, j)$ be the next higher combinations of (i, j): $\{(i, j + 1), (i+1, j)\}$, and $N^-(i, j)$ be the next lower combinations of (i, j): $\{(i-1, j), (i, j - 1)\}$. The notation $\bar{*}$ means the complementary set. For example, $\bar{B}$ is the set of combinations which have not been tested.

One-dimensional Search.

As shown in Figure 1, if the current dose combination (i, j) is rejected, dose deescalation is required. If $N^-(i, j) \cap \bar{R} \cap \bar{B}$ is empty, Stage 1 is ended. Otherwise, a patient will be enrolled and assigned to each combination in this set.

On the other hand, if the current dose combination (i, j) is retained, dose escalation is required. If $N^+(i, j) \cap \bar{R} \cap \bar{B}$ is empty, Stage 1 is ended. If only one dose combination remains in this set, it is the one to be tested. Otherwise, if both $(i, j + 1), (i + 1, j)$ remain in this set, the search will move in the direction with the larger gap between DLT probabilities of consecutive doses. For example, $(i + 1, j)$ will be the next dose combination to be tested, if $\hat{p}_{ij} - \hat{p}_{(i-1)j} > \hat{p}_{ij} - \hat{p}_{i(j-1)}$. If they are tied, both combinations $(i, j + 1), (i + 1, j)$ will be tested and it becomes a two-dimensional search.

Two-dimensional Search.

As shown in Figure 2, if both dose combinations in $N^+(i, j)$ are rejected, dose deescalation is required for both agents. If $\{(i + 1, j - 1), (i - 1, j + 1)\} \cap \bar{R} \cap \bar{B}$

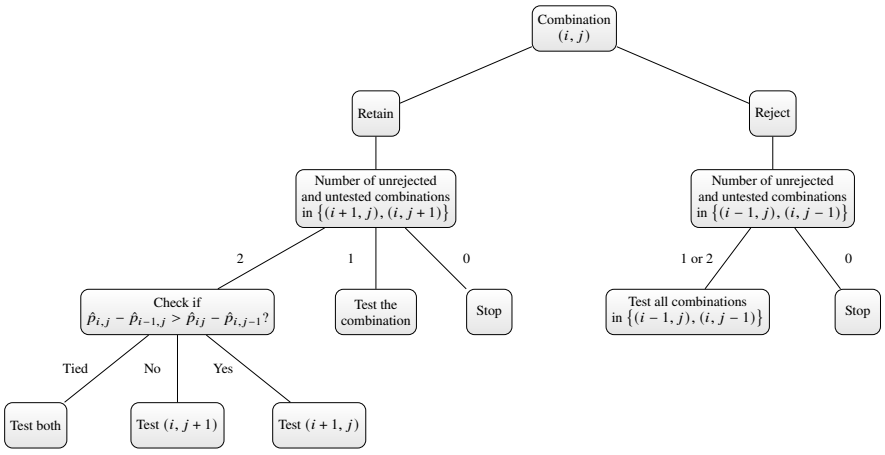


Fig. 1 Finding MTD for two agents, one DLT case: rule-based, one dimensional search

is empty, Stage 1 is ended. Otherwise, a patient will be enrolled and assigned to each combination in this set. Note that it is possible to initiate two one-dimensional searches, at $(i+1, j-1)$ and at $(i-1, j+1)$. If simplicity is desired, we can proceed only in the direction with the larger gap between DLT probabilities of consecutive doses. For example, a one-dimensional search will begin only at $(i+1, j)$, if $\hat{p}_{(i+1)j} - \hat{p}_{ij} > \hat{p}_{i(j+1)} - \hat{p}_{ij}$. If they are tied, we can randomly select one of them to initiate the one-dimensional search.

On the other hand, if both dose combinations in $N^+(i, j)$ are retained, dose escalation is required for both agents. If $(i+1, j+1)$ is neither tested nor rejected, it is the next one to be tested. Otherwise, Stage 1 is ended.

In case where only one in $N^+(i, j)$, say $(i, j+1)$, is retained, if $(i, j+1)$ is neither tested nor rejected, it is the next one to be tested. Otherwise, Stage 1 is ended.

Where the search starts is controversial. For conservative investigators, the lowest combination $(1, 1)$ is recommended. This design was published [10] and will be referred to as data-driven 2+1+3 design in the later sections. We defer the examples in Section 5.

3.2 A Rule-Based Design for Agents with Non-Overlapping Dose-Limiting Toxicities

There has been a growing trend in combining targeted antitumor agents with cytotoxic counterparts to enhance the efficacy of cancer treatment. Examples of such synergistic combinations include bevacizumab (as the targeted agent) and paclitaxel

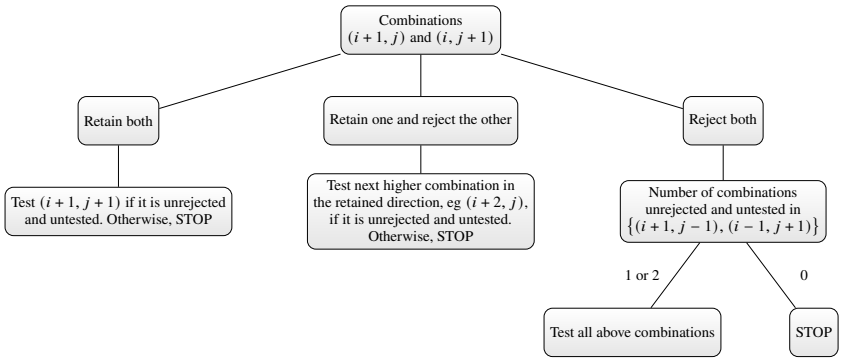


Fig. 2 Finding MTD for two agents, one DLT case: rule-based, two dimensional search

(as the cytotoxic agent), as well as cetuximab (targeted agent) and irinotecan (cytotoxic agent). Targeted agents often display distinct toxicity profiles when compared to cytotoxic agents, a characteristic that can be leveraged to increase the safety of patients in clinical trials while maintaining a reasonable sample size. This section presents a rule-based design that incorporates the source of DLTs to guide dose escalations and de-escalations [11].

3.2.1 Safety-Driven A+B+C Design

Our design is a modification of the A+B+C design [12], the decision rules of which are illustrated in Figure 3. For a given dose combination, (i, j), up to three cohorts of patients comprising A, B, and C patients are enrolled and assigned to the dose combination. Let n_A denote the number of patients who develop DLTs in the cohort of A patients, with n_B and n_C similarly defined. Within each cohort, a pair of preselected thresholds determines whether (i, j) is accepted, rejected, or an additional cohort of patients is enrolled. For example, in the first cohort of A patients, the thresholds are denoted a_e and a_d, where the subscripts 'e' and 'd' denote escalate and de-escalate, respectively. If $n_A \leq a_e$, (i, j) is accepted as an MTD candidate; if $a_e < n_A < a_d$, a second cohort of B patients is enrolled and assigned to (i, j); and if $n_A \geq a_d$, (i, j) is rejected as an MTD candidate.

In each cohort of patients, an observed DLT is classified into one of three types: Type A, if the clinician judges that the DLT is caused by agent A and not agent B; Type B, if the opposite is true; and Type U, if the clinician is unable to make a definitive judgement because the DLT is common to both agents. The toxicity outcome of a patient treated at combination (i, j) can be represented as a triplet, $(t_{ij}^{\mathrm{A}}, t_{ij}^{\mathrm{B}}, t_{ij}^{\mathrm{U}})$, where

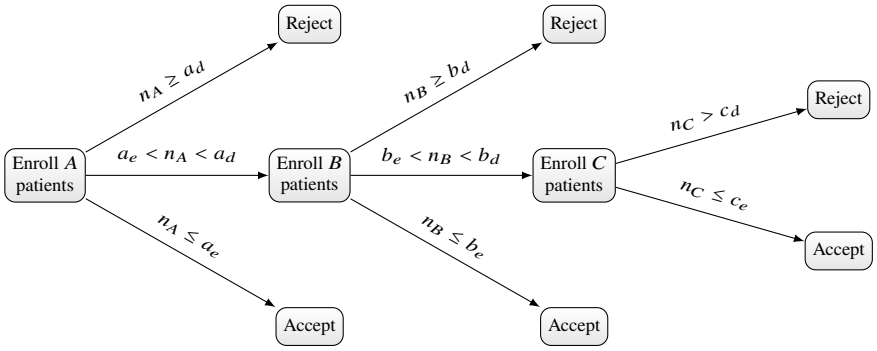


Fig. 3 Dose decision rules for the A+B+C design. Here, n_A, n_B, and n_C are the number of patients who develop DLTs in each respective cohort, while a_e, a_d, b_e, b_d, c_e, and c_d are pre-selected thresholds.

$$t_{ij}^{\mathrm{A}} = \begin{cases} 1 & \text{if there is a DLT of Type A,} \\ 0 & \text{otherwise,} \end{cases}$$

and t_{ij}^{B} and t_{ij}^{U} are similarly defined. If the current dose combination, (i, j), is rejected by an A+B+C design and de-escalation is indicated, we propose de-escalating from (i, j) to $(i-1, j)$ when $\sum t_{ij}^{\mathrm{A}}$ exceeds $\sum t_{ij}^{\mathrm{B}}$, where the summations are over all patients treated at (i, j). Similarly, we recommend de-escalating from (i, j) to $(i, j-1)$ when $\sum t_{ij}^{\mathrm{A}}$ is less than $\sum t_{ij}^{\mathrm{B}}$. In cases where $\sum t_{ij}^{\mathrm{A}}$ equals $\sum t_{ij}^{\mathrm{B}}$, the choice between $(i-1, j)$ and $(i, j-1)$ is randomized. Furthermore, upon the rejection of the current dose combination, all dose combinations with a higher partial order are also rejected. If, on the other hand, (i, j) is accepted as an MTD candidate and escalation is indicated, we suggest increasing the dose of the agent with a lower number of attributed DLTs.

The stopping rules for our design are as follows.

1. Escalation is no longer possible, either because the current accepted dose combination is the highest dose combination or all conjunctive combinations of a higher partial order have been previously rejected.
2. De-escalation is no longer possible because the current dose combination is the starting dose combination.
3. The de-escalated dose combination has previously been accepted.

If a trial is stopped based on rule (2), no MTD is recommended. Otherwise, the dose combination with the highest partial order is recommended as an MTD. In some situations, two MTDs are recommended. Figure 4 illustrates a hypothetical trial which recommends $(2, 2)$ and $(4, 1)$ as MTDs. These two dose combinations cannot be ordered in terms of toxicity, and each has a higher order than other accepted combinations.

Lee and Fan (2012) compared the operating characteristics of the safety-driven A+B+C design to those of the original A+B+C design [12]. The simulation results

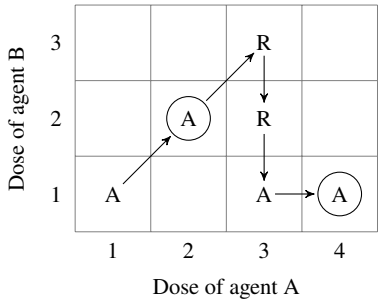


Fig. 4 A hypothetical trial that recommends two maximum tolerated dose combinations, indicated by a circle. Here, 'A' and 'R' denote accept and reject, respectively, of a dose combination as an MTD candidate.

suggest that by incorporating the source of DLTs to guide dose escalations and de-escalations, the A+B+C design, especially the relatively aggressive 2+1+3 design, is less likely to overestimate the MTD. In fact, the dissimilarities in the choices of MTD between the 2+1+3 design and the comparatively conservative 4+4+4 design diminished.

3.2.2 A Hybrid Design

When a combination, (i, j), is accepted as an MTD candidate, there is an alternative escalating strategy: rather than escalating only the dose of the agent with fewer attributed DLTs, as previously suggested, the doses of both agents are increased to $(i + 1, j + 1)$. This 'fast' escalation approach is designed to minimize the number of patients receiving sub-therapeutic treatment due to protracted escalations from a conservative starting dose. To moderate a fast escalation and thereby mitigate the risk of exposing patients to excessively toxic combinations, one can adopt a more conservative A+B+C design when assessing an escalated dose combination. For example, Lee and Fan (2012) demonstrate that adopting a 3+3+3 design for de-escalations and a 4+4+4 design for escalations offer a good compromise between sample size and power.

3.3 A Curve-Free Bayesian Adaptive Design

One way to study many dose combinations with a small sample that is typical in phase I trials is to incorporate prior information for the agents. The Bayesian paradigm offers a coherent framework to do so. The key components of a Bayesian decision-theoretic design are: (1) a probability model that quantifies the uncertainties about the toxicity response at each dose as well as the associated DLT probabilities, (2) a utility function that quantifies the desirability of a given dose allocation decision, and (3) a set of rules for deciding when to stop a trial. This section presents a Bayesian decision-theoretic design for two-agent phase I trials that is relatively

easy for clinicians to understand and implement, yet performs comparably to more complex designs [13] .

3.3.1 Probability Model

Let t_{ij} denote the binary outcome of a patient treated at dose combination (i, j), where $t_{ij} = 1$ if the patient experiences a DLT and $t_{ij} = 0$ otherwise. We model the sampling distribution of t_{ij} as $\text{Ber}(p_{ij})$, where p_{ij} is the unknown DLT probability at dose combination (i, j), and the prior distribution of p_{ij} as $\text{Beta}(a_{ij}, b_{ij})$, where a_{ij} and b_{ij} are hyperparameters that remain to be specified.

Specifying the Prior Distribution

We recall that a $\text{Beta}(a_{ij}, b_{ij})$ distribution can be characterized by its mean,

$$\mu_{ij} = \frac{a_{ij}}{a_{ij} + b_{ij}}, \tag{1}$$

and a pair of quantiles, $(q_{ij}^{\text{L}}, q_{ij}^{\text{U}})$. In other words, (a_{ij}, b_{ij}) can be uniquely determined by $(\mu_{ij}, q_{ij}^{\text{L}}, q_{ij}^{\text{U}})$, which may be elicited as follows.

Prior means. Ideally, the clinician is able to provide prior estimates of μ_{ij}, denoted μ_{ij}^0, which should preserve the partial order in toxicity: $\mu_{ij}^0 < \mu_{rs}^0$ whenever $(i, j) \prec (r, s)$. The findings from single-agent trials may serve as a reference: let $\hat{p}_{\text{A}_i}$ and $\hat{p}_{\text{B}_j}$ denote the estimated DLT probabilities of agent A at dose i and agent B at dose j, respectively, from single-agent trials. A preliminary estimate of μ_{ij} is given by

$$\tilde{\mu}_{ij} = 1 - \hat{\Pr}(\text{no DLT from either agent}) = 1 - (1 - \hat{p}_{\text{A}_i})(1 - \hat{p}_{\text{B}_i}), \tag{2}$$

based on the assumption that the DLT of the two agents are independent. These estimates may not preserve the partial order in toxicity, in which case the clinician should adjust the estimates, and the resulting values will serve as μ_{ij}^0.

Prior quantiles. Since quartiles are generally easy to understand, we propose eliciting the first and third quartiles from the clinician. That is, the quantiles, q_{ij}^{L} and q_{ij}^{U}, satisfy

$$\Pr(p_{ij} \le q_{ij}^{\text{L}}) = \Pr(p_{ij} \ge q_{ij}^{\text{U}}) = 0.25. \tag{3}$$

To facilitate the process, we can generate several candidates for $(q_{ij}^{\text{L}}, q_{ij}^{\text{U}})$ for each dose combination, and ask the clinician to select a pair that best represent his or her belief. The candidates are generated as follows. If $\mu_{ij}^0 \ge 0.5$, we fix $a_{ij}^0 = 1, 2, \ldots$ and solve for the corresponding b_{ij}^0 using equation (1); otherwise, we fix $b_{ij}^0 = 1, 2, \ldots$ and solve for the corresponding a_{ij}^0 using equation (1). The resulting (a_{ij}^0, b_{ij}^0) are used to solve for $(q_{ij}^{\text{L}}, q_{ij}^{\text{U}})$. A numerical illustration

Table 3 Example of pairs of first and third quartiles, $(q_{ij}^{\mathrm{L}}, q_{ij}^{\mathrm{U}})$, presented to the clinician for prior elicitation. The pairs are generated according to whether the prior mean, μ_{ij}^0, is greater or equal to 0.5.

$\mu_{ij}^0 = 0.65$			$\mu_{ij}^0 = 0.35$		
a_{ij}^0	b_{ij}^0	$(q_{ij}^{\mathrm{L}}, q_{ij}^{\mathrm{U}})$	a_{ij}^0	b_{ij}^0	$(q_{ij}^{\mathrm{L}}, q_{ij}^{\mathrm{U}})$
1	0.54	(0.41, 0.92)	0.54	1	(0.08, 0.59)
2	1.08	(0.48, 0.85)	1.08	2	(0.15, 0.52)
3	1.62	(0.51, 0.81)	1.62	3	(0.19, 0.49)
⋮	⋮	⋮	⋮	⋮	⋮

is given in Table 3. The reason for generating $(q_{ij}^{\mathrm{L}}, q_{ij}^{\mathrm{U}})$ according to whether $\mu_{ij}^0 \geq 0.5$ or $\mu_{ij}^0 < 0.5$ is to ensure that a_{ij}^0 and b_{ij}^0 are small so that the prior is not overly informative.

Calculating the Posterior Distribution

Suppose a cohort of n_{ij} patients have been treated at dose combination (i, j). We extend the observed data according to the method described in Section 2 for one-agent trials. Specifically, under the assumption that $p_{ij} < p_{rs}$ whenever $(i, j) \prec (r, s)$, patients who experienced a DLT at (i, j) are expected to do so when treated at (r, s) for $(i, j) \prec (r, s)$; likewise, patients who tolerated (i, j) are expected to do so when treated at (r, s) for $(r, s) \prec (i, j)$. For example, consider a study of combinations of $I = 3$ doses of agent A and $J = 4$ doses of agent B. If a patient experienced a DLT at $(2, 3)$, the working data for this patient consist of a DLT at $(2, 3)$, $(2, 4)$, $(3, 3)$, $(3, 4)$, $(4, 3)$, and $(4, 4)$; in the absence of DLT, the working data consist of no DLT at $(2, 3)$, $(2, 2)$, $(2, 1)$, $(1, 3)$, $(1, 2)$, and $(1, 1)$. Having extended the data, the prior distributions, $\mathrm{Beta}(a_{rs}^0, b_{rs}^0)$, are updated to give the posterior distributions, $\mathrm{Beta}(a_{rs}, b_{rs})$, where a_{rs} and b_{rs} are calculated as follows.

1. If $(r, s) = (i, j)$, then $a_{rs} = a_{rs}^0 + \sum t_{ij}$ and $b_{rs} = b_{rs}^0 + n_{ij} - \sum t_{ij}$.
2. If $(i, j) \prec (r, s)$, then $a_{rs} = a_{rs}^0 + \sum t_{ij}$ and $b_{rs} = b_{rs}^0$.
3. If $(r, s) \prec (i, j)$, $a_{rs} = a_{rs}^0$ and $b_{rs} = b_{rs}^0 + n_{ij} - \sum t_{ij}$.
4. If (r, s) and (i, j) are not comparable, then $a_{rs} = a_{rs}^0$ and $b_{rs} = b_{rs}^0$.

3.3.2 Dose Allocation and Utility Function

To obtain preliminary data, we treat the first cohort of patients at the lowest dose combination, and then randomly escalate the dose of one agent for subsequent cohorts until the first toxicity is observed or the highest dose combination is reached,

whichever occurs earlier. Afterward, we switch to the following decision-theoretic approach.

Central to the decision-theoretic approach is a utility function which measures the values of various dose allocation decisions. A dose allocation is considered optimal if it maximizes the expected utility with respect to the posterior distribution of the unknown DLT probabilities. Formally, let θ_{T} be the target DLT probability and $u_k(p_{ij}, \theta_{\mathrm{T}})$ be the utility of assigning the kth patient to dose combination (i, j). A (total) utility function for dose allocation, in the simplest form, can be expressed as

$$u(p_{ij}, \theta_{\mathrm{T}}) = \sum u_k(p_{ij}, \theta_{\mathrm{T}}).$$

An example of utility function for a single patient, $u_k(p_{ij}, \theta_{\mathrm{T}})$, is

$$u_k(p_{ij}, \theta_{\mathrm{T}}) = \begin{cases} -\alpha_0(\theta_{\mathrm{T}} - p_{ij}) & \text{if } p_{ij} \leq \theta_{\mathrm{T}} \\ -\eta_0(p_{ij} - \theta_{\mathrm{T}}) & \text{if } p_{ij} > \theta_{\mathrm{T}}, \end{cases} \tag{4}$$

where α_0 and η_0 are specified positive constants. This function assigns a negative value to the selection of dose combinations with a DLT probability different from θ_{T}, and it has the flexibility of allowing for the utility of overdosing to decrease faster than that of underdosing (by setting $\eta_0 > \alpha_0$) when patient safety is a primary concern.

In practice, finding the optimal dose allocation is computationally expensive, if not infeasible. For this reason, myopic strategies, such as one-step-look-ahead (OSLA), are often used instead. With the OSLA strategy, we act as if the next patient were the last patient of the study, so that the next dose allocation is based on the current posterior distribution. Specifically, for the $(k + 1)$th patient, the expected utility function corresponding to the OSLA strategy is proportional to the conditional expectation of $u_{k+1}(p, \theta_{\mathrm{T}})$, given all data collected up to the kth patient. This results in a considerable simplification of the maximization problem. To illustrate, consider cohort sizes of one patient, so that $u(p, \theta_{\mathrm{T}}) = u_{k+1}(p, \theta_{\mathrm{T}})$. Let $f(p; a_{ij}, b_{ij})$ denote the probability density function of a Beta(a_{ij}, b_{ij}) distribution, where a_{ij} and b_{ij} are the parameters of the posterior distribution for p_{ij}. Then, with the utility function given in equation 4,

$$\begin{aligned}
&\mathrm{E}\left[u(p, \theta_{\mathrm{T}}) \,\middle|\, a_{ij}, b_{ij}\right] \\
&= \int_0^{\theta_{\mathrm{T}}} -\alpha_0(\theta_{\mathrm{T}} - p) f(p; a_{ij}, b_{ij}) \,\mathrm{d}p + \int_{\theta_{\mathrm{T}}}^1 -\eta_0(p - \theta_{\mathrm{T}}) f(p; a_{ij}, b_{ij}) \,\mathrm{d}p \\
&= -(\alpha_0 + \eta_0) \left[\theta_{\mathrm{T}} F(\theta_{\mathrm{T}}; a_{ij}, b_{ij}) - \left(\frac{a_{ij}}{a_{ij} + b_{ij}}\right) F(\theta_{\mathrm{T}}; a_{ij} + 1, b_{ij})\right] \\
&\qquad -\eta_0 \left[\left(\frac{a_{ij}}{a_{ij} + b_{ij}}\right) - \theta_{\mathrm{T}}\right],
\end{aligned}$$

where $F(\theta_T; a_{ij}, b_{ij}) = \int_0^{\theta_T} f(p; a_{ij}, b_{ij})\,\mathrm{d}p$. This can be easily evaluated using standard statistical software.

Having calculated the expected utility function, the next dose assignment is given by the combination which yields the highest expected utility. In some clinical trials, a conservative dose escalation strategy that prohibits dose skipping may be preferred. In this case, if the current dose combination is (r, s), the next dose allocation is limited to dose combinations (i, j) such that $i \leq r$ and $j \leq s$, as well as the combinations $(r + 1, s)$ and $(r, s + 1)$.

3.3.3 Stopping Rules

Before the trial begins, the minimum and maximum sample sizes, denoted $n_{\min}$ and $n_{\max}$ respectively, are specified. In addition, let $\delta_0 \geq 0$ be specified such that $\theta_T + \delta_0$ is an upper bound on the acceptable DLT probabilities. The following rules determine when to stop a trial.

1. To mitigate the effects of prior misspecification, early stopping is prohibited before the sample size reaches $n_{\min}$.
2. The trial is stopped when the sample size reaches $n_{\max}$.
3. The trial is stopped if $\Pr(p_{11} > \theta_T + \delta_0 \,|\, \text{data}) > r_1$ for some prespecified r_1, the probability that the lowest (and hence all) dose combinations are likely to be overly toxic.
4. If (i, j) is the current selected dose combination, the trial is stopped if

$$\min_{(i,j)<(r,s)} \Pr(p_{rs} > \theta_T + \delta_0 \,|\, \text{data}) > r_2$$

   for some prespecified r_2, the probability that all dose combinations of higher partial order than the current dose combination are likely to be overly toxic.
5. Rule 1 supersedes rules 3 and 4.

If a trial is stopped based on rule 3, then no MTD is recommended. Otherwise, the current dose combination is recommended as an MTD.

4 Biological Efficacious Doses in One-Agent Trials

In this section, we will propose two curve-free designs of finding biological efficacious doses in one-agent trials. For phase Ia/Ib trials in which both DLT outcome and efficacy response/signal are observed, biological efficacious doses (BEDs) are to be identified. A BED is a "safe" dose that demonstrates a certain level of biological effect.

No parametric models (curves) are assumed to govern the dose-DLT and dose-efficacy relationships. We assume that the dose-DLT curve is monotonic non-decreasing as CBA design, while the dose-efficacy curve is unimodal. Therefore,

MTD is not necessary to be the biological optimal dose (BOD). While BOD is the target dose for many other designs, our primary goal is to identify all BEDs - they may not have the optimal biological effect but they have a desirable biological effect and acceptable toxicity profile. Because of the unimodal shape of dose-efficacy curve, the set of BEDs is formed as an interval and the objective of our design is to identify this interval, referred to as the BED interval.

4.1 The General Design

In the first stage (phase Ia), we adopt the CBA design to locate MTD quickly. After a MTD is found, the trial moves to the second stage (phase Ib), the goal of which is to identify the BED interval. In the second stage, we continue to monitor the toxicity profile and update the MTD. Only the admissible doses, those not exceeding the current MTD, are considered in the search for the BED interval. Because phase Ib trials typically have small sample sizes, the efficacy rate for each individual dose cannot be reliably estimated and much harder for statistical inferences. Therefore, the proposed design groups adjacent doses and models the (unimodal) dose-efficacy relationship using a step function: all possible groupings of adjacent doses, subject to a maximum of three groups, are considered. A utility function is proposed to measure the goodness of fit of each step function, and an interval associated with the best fitting step function is recommended as the BED interval.

4.2 Modeling DLT and Efficacy Probabilities

Let the dose levels be indicated in discrete integers i for $i = 1, ..., k$. Let $p_{T,i}$ and $p_{E,i}$ be the DLT and efficacy probabilities, respectively, of dose i. We assume that the DLT probabilities are monotonic non-decreasing, that is, $p_{T,1} \leq p_{T,2} \leq ... \leq p_{T,k}$; it follows that all doses not exceeding the MTD are admissible. The prior distributions of $p_{T,i}$, for $i = 1, ..., k$ are assumed to be independent beta distributions $\text{Beta}(a_i^0, b_i^0)$. The initial Beta parameters, a_i^0, b_i^0, for $i = 1, ..., k$, are chosen such that the monotonic non-decreasing property of prior means holds: $\mu_{T,1}^0 \leq \mu_{T,2}^0 \leq ... \leq \mu_{T,m}^0$, where $\mu_{T,i}^0 = a_i^0/(a_i^0 + b_i^0)$. Please refer to Section 2.1 for the prior parameter settings.

While it is reasonable to assume that the DLT probability is monotonic non-decreasing in dose, this assumption may not be tenable for the efficacy. Instead, we assume that the efficacy curve is unimodal: it increases at low dose levels and plateaus or even decreases at higher levels. We model the unimodal efficacy curve using a step function:

$$p_{E,i} = \begin{cases} p_L \text{ for } i \in [1, L-1], \\ p_B \text{ for } i \in [L, U], \\ p_U \text{ for } i \in [U+1, k], \end{cases} \tag{5}$$

where p_L, p_B, p_U are the "pooled" efficacy probabilities of the doses in the corresponding intervals, and L and U are doses with $L, U \in \{1, \ldots, k\}$ and $L \leq U$. Due to the unimodal shape of the efficacy curve, the middle interval $B = [L, U]$ contains the most efficacious doses and if the BED interval exists, it is embedded within the interval B.

The step function model that can accommodate a variety of scenarios: when $L = U$, there is one dose with optimal efficacy probability; when $L = 1$ and $U = k$, all doses have the optimal efficacy probability; when $L = 1$ and $U < k$, the lower doses are more efficacious than the higher doses; when $L > 1$ and $U = k$, the higher doses are more efficacious than the lower doses; and when $L > 1$ and $L < U < k$, there are multiple doses in the middle with optimal efficacy probability.

The prior distribution of the efficacy rate at each dose level is taken to be independent beta distributions, that is, we have $p_{E,i}$ independently distributed as $\text{Beta}(\alpha_i^0, \beta_i^0)$ for $i = 1, ..., m$. We defer the discussion of the specification of the parameters a_i^0, b_i^0, α_i^0, and β_i^0, $i = 1, \ldots, m$, to Section 3.

4.3 Utility Functions

Let θ_{T} be the maximum tolerable DLT probability and θ_{E} be the minimum acceptable efficacy probability. Recall that doses with tolerable DLT probability and acceptable efficacy probability are BEDs. The first step towards identifying the BED interval is to determine the "best" fitting step function among those generated from different choices of L and U. It seems reasonable to measure the goodness of fit of a step function by how well it distinguishes the BEDs and non-BEDs. In other words, if a dose is a BED, it should be included in the interval $B = [L, U]$. The successful inclusion of this dose should be assigned a gain, and the gain should increase for a more efficacious dose. On the other hand, if a dose is not a BED, it should be excluded in the interval B. The successful exclusion of this dose should be assigned a gain, and the gain should increase for a less efficacious dose.

With the above concept, we define the utility of an interval B at dose i by

$$u_i(B, \theta_{\text{E}}) = \begin{cases} \mathbb{1}_{\{p_{E,i} \geq \theta_{\text{E}}\}} [a + c(p_{E,i} - \theta_{\text{E}})] \text{ for } i \in B, \\ \mathbb{1}_{\{p_{E,i} < \theta_{\text{E}}\}} [b + d(\theta_{\text{E}} - p_{E,i})] \text{ for } i \notin B, \end{cases} \tag{6}$$

where $\mathbb{1}_{condition}$ takes the value 1 if $condition$ is true and 0 otherwise. The positive constants a, b are the gains for the correct inclusion or exclusion of this dose, respectively, and the others c, d are the weights for the degree to which this dose is more or less efficacious than the minimal acceptable efficacy probability θ_{E}, respectively.

The total utility is the weighted sum of the utilities at all admissible doses:

$$u(B, \theta_{\mathrm{E}}) = \sum_{i=1}^{\mathrm{MTD}} w_i * u_i(B, \theta_{\mathrm{E}}). \tag{7}$$

An intuitive choice of the weight w_i is the sample size at dose i, denoted n_i, but it can be chosen in other ways.

Let e_i be the number of efficacy responses among the n_i patients treated at dose d_i. The posterior distribution of $p_{E,i}$ is $\mathrm{Beta}(\alpha_i = \alpha_i^0 + e_i, \beta_i = \beta_i^0 + n_i - e_i)$, and the expected utility at dose i is given by

$$\begin{aligned}
&\mathrm{E}[u_i(B, \theta_{\mathrm{E}})] \\
&= \begin{cases} (a - c\theta_{\mathrm{E}})[1 - I_{\theta_{\mathrm{E}}}(\alpha_i, \beta_i)] + c\frac{\alpha_i}{\alpha_i+\beta_i}[1 - I_{\theta_{\mathrm{E}}}(\alpha_i + 1, \beta_i)] & \text{for } i \in B, \\ (b + d\theta_{\mathrm{E}})I_{\theta_{\mathrm{E}}}(\alpha_i, \beta_i) - d\frac{\alpha_i}{\alpha_i+\beta_i} I_{\theta_{\mathrm{E}}}(\alpha_i + 1, \beta_i) & \text{for } i \notin B, \end{cases}
\end{aligned}$$

where $I_x(\alpha, \beta)$ is the regularized incomplete beta function. It follows that there is an analytical expression for the expected total utility of a step function: $\mathrm{E}[u(B, \theta_{\mathrm{E}})] = \sum_i w_i \mathrm{E}[u_i(B, \theta_{\mathrm{E}})]$, where B is the interval that identifies the step function. We refer to the step function that maximizes the expected total utility as the optimal step function. Let B^* denote the interval associated with the maximum of the optimal step function.

By the definition of the total utility function, the optimal step function is one that provides the maximum separation between the BEDs and non-BEDs, in the sense that doses with the highest efficacy rates are grouped into the interval B^*. Therefore, if the BED interval exists, it will be B^*. However, due to the limit of sample size, we might not be able to identify B^* correctly. Therefore, we will exclude the non-BEDs from the recommended B^*, denoted as $\hat{B}^*$, as follows.

Let A be a subinterval of $\hat{B}^*$ obtained by excluding one or more lower and/or higher dose levels in $\hat{B}^*$, and let h be the number of dose levels in A. Next, we define the efficacy probability of A as the mean efficacy probability $p_A = \sum_{i \in A} p_{E,i}/h$, and we set the initial prior distribution of p_A as the beta distribution with mean initial parameters: $\mathrm{Beta}(\alpha_A^0 = \sum_{i \in A} \alpha_i^0/h, \beta_A^0 = \sum_{i \in A} \beta_i^0/h)$. Upon the collection of data, the posterior distribution of p_A becomes $\mathrm{Beta}(\alpha_A = \alpha_A^0 + \sum_{i \in A} e_i/h, \beta_A = \beta_A^0 + \sum_{i \in A}(n_i - e_i)/h)$, and the posterior probability that A is acceptable is given by $P(p_A \geq \pi_E) = 1 - I_{\pi_E}(\alpha_A, \beta_A)$. The proposed design recommends the subinterval that maximizes this posterior probability as the BED interval.

4.4 Dose Selection Rules

There are two sets of dose selection rules corresponding to the two stages in the proposed design. In the first stage, we adopted CBA design (Section 2) to locate the MTD quickly. If the CBA design recommends a MTD within a pre-set maximal sample size of the first stage, the trial moves to the second stage: identify the BED interval. In this stage, we continue to monitor DLT outcomes to ensure patient safety

and update MTD after each cohort. Only admissible doses will be assigned to the patients. The detailed dose selection rules for the second stage are given as follows:

(i) We update the MTD using the CBA design and search for the BED interval, $A = [L^*, U^*]$, as described in Section 4.3. Upon identifying A, we assign a patient to each admissible dose between $L^* - 1$ and $U^* + 1$, inclusive.
(ii) Step (i) is repeated until the sample size is at least n_{min} and one of the following stopping rules applies:

   a. If the maximum sample size of a trial is reached, the trial is terminated.
   b. If the current recommended interval, A, is very likely to be acceptable, that is, $P(p_A \geq \theta_E) \geq q$, the trial is terminated and we recommend A as the BED interval.
   c. If all admissible doses are very likely to be unacceptable, that is, $P(p_{E,i} < \theta_E) \geq q$ for $i \in [1, \text{MTD}]$, the trial is terminated and we conclude that there is no BED.

If the trial is terminated before reaching the maximum sample size, there are three possible conclusions: 1) the MTD is below the first dose 2) there is no BED or 3) the BED interval has been identified. If the trial reaches the maximum sample size, the final interval A needs to be examined for its acceptance: if A is highly likely to be unacceptable, that is, $P(p_A < \theta_E) \geq q$, we conclude that there is no BED interval; otherwise, we recommend the interval A as the BED interval.

This proposed design will be referred to as CFBD, which stands for **c**urve-**f**ree **B**ayesian **d**esign. Figure 5 presents its flowchart for illustration.

4.5 Frequentist Version of the BED-Finding Stage

When there is little or no prior information on the efficacy probabilities, a vague or reference prior can be used. However, there is limited guidance on which vague prior should be used and some researchers may prefer a frequentist approach instead. This prompts us to propose a frequentist version of the second stage of the proposed design. Consider a step function as defined in eq. 5. The pooled efficacy probabilities, p_L, p_B, p_U, can be estimated empirically. For instance, if the upper limit U is less than MTD, the pooled efficacy probabilities for the intervals $[1, L-1]$, $[L, U]$, and $[U+1, \text{MTD}]$ are estimated by:

$$\hat{p}_L = \sum_{i=1}^{L-1} e_i / \sum_{i=1}^{L-1} n_i, \quad \hat{p}_B = \sum_{i=L}^{U} e_i / \sum_{i=L}^{U} n_i, \quad \hat{p}_U = \sum_{i=U+1}^{\text{MTD}} e_i / \sum_{i=U+1}^{\text{MTD}} n_i,$$

respectively. Because we would like to include as many BEDs as possible, the longest interval $B = [L, U]$ is desired. Therefore, only step functions with $\hat{p}_L, \hat{p}_U < \theta_E$ and $\hat{p}_B \geq \theta_E$ are considered. Such step functions are referred to as acceptable step functions later.

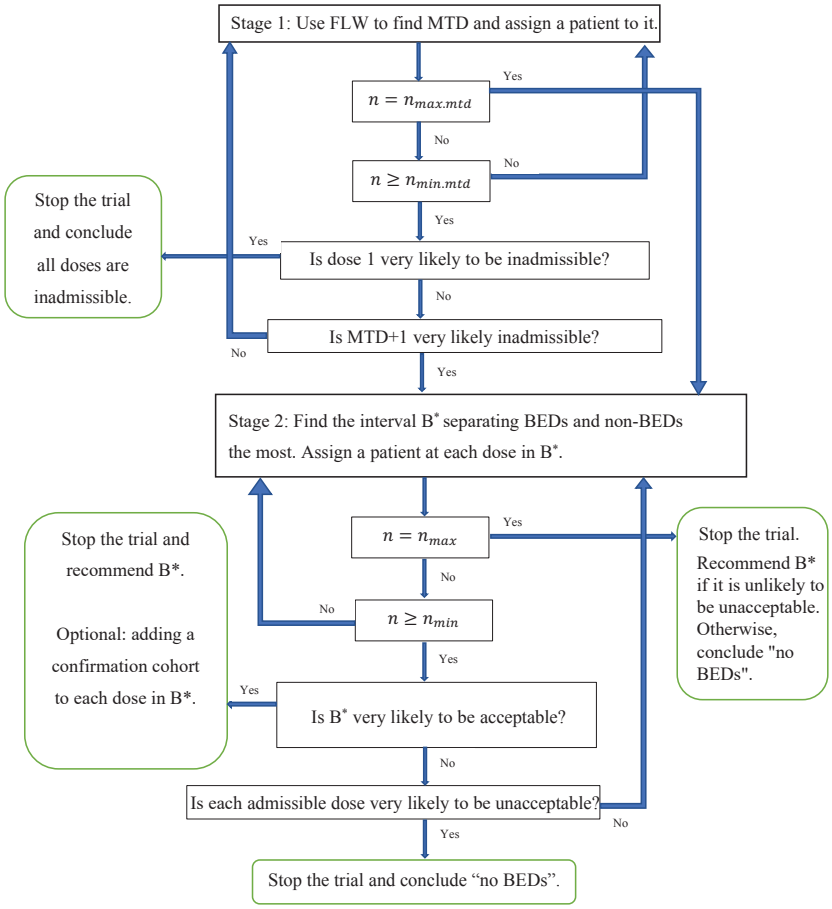


Fig. 5 Finding BEDs: flowchart of the 2-stage curve-free Bayesian or hybrid design

The utility of a step function at dose i can be calculated by substituting p_{Ei} with its sample proportion, e_i/n_i, in $u_i(B, \theta_E)$ eq. 6. Then the total utility of a step function can be calculated as their weighted sum: $u(B, \theta_E) = \sum n_i u_i(B, \theta_E)$.

The dose selection rules in stage two are revised as follows:

(i) We update the MTD using the CBA algorithm and find the acceptable step function that maximizes the total utility, referred to as the optimal step function. Denote the interval associated with the optimal step function by $\hat{B}^* = [L^*, U^*]$.

   a. If $\hat{B}^*$ exists, the trial assigns a patient to each admissible dose between $L^* - 1$ and $U^* + 1$, inclusive.

b. If $\hat{B}^*$ does not exist, that is, there is no acceptable step function, the trial assigns a patient to every admissible dose.

(ii) Step (i) is repeated until the sample size is at least n_{min} and one of the following stopping rules applies:

a. If the maximum sample size of a trial is reached, the trial is terminated. If $\hat{B}^*$ exists, we recommend it as the BED interval; otherwise, we conclude that there is no BED.

b. If $\hat{B}^*$ exists and its efficacy probability is acceptable, the trial is terminated and we conclude $\hat{B}^*$ is the BED interval. The interval $\hat{B}^*$ is called acceptable if its sample size, $n_{\hat{B}^*} = \sum_{i=L^*}^{U^*} n_i$, exceeds ten and the $(1-\alpha)$ Wilson upper-tailed confidence interval of its efficacy $p_{\hat{B}^*}$ is strictly above the minimum efficacy θ_{E}. Note that the formula of the upper-tailed confidence interval is:

$$\left[\hat{p} - z_\alpha \sqrt{\hat{p}(1-\hat{p})/(n_{\hat{B}^*}+4)}, 1\right],$$

where $\hat{p} = (\sum_{i=L^*}^{U^*} e_i + 2)/(n_{\hat{B}^*}+4)$.

c. If $\hat{B}^*$ does not exist and all admissible doses (less than or equal to MTD) are unacceptable, the trial is terminated and we conclude that there is no BED. A dose i is called unacceptable if its sample size n_i exceeds ten and the $(1-\alpha)$ Wilson lower-tailed confidence interval of its efficacy $p_{E,i}$ is strictly below the minimum efficacy θ_{E}. Note that the formula of the lower-tailed confidence interval is:

$$\left[0, \hat{p} + z_\alpha \sqrt{\hat{p}(1-\hat{p})/(n_i+4)}\right],$$

where $\hat{p} = (e_i + 2)/(n_i + 4)$.

When the second stage of CFBD is replaced with the frequentist version, we refer to the design as CFHD, where "H" stands for hybrid.

After the BED interval has been recommended, a confirmation cohort could be added to each dose in the BED interval to increase the precision of the estimate of the efficacy probability of the BED interval. The MTD and BED interval will be updated after collecting data from the confirmation cohorts. The point estimate, together with confidence interval of the efficacy probability of the BED interval can be provided to help clinicians select a dose to move forward to phase II trials.

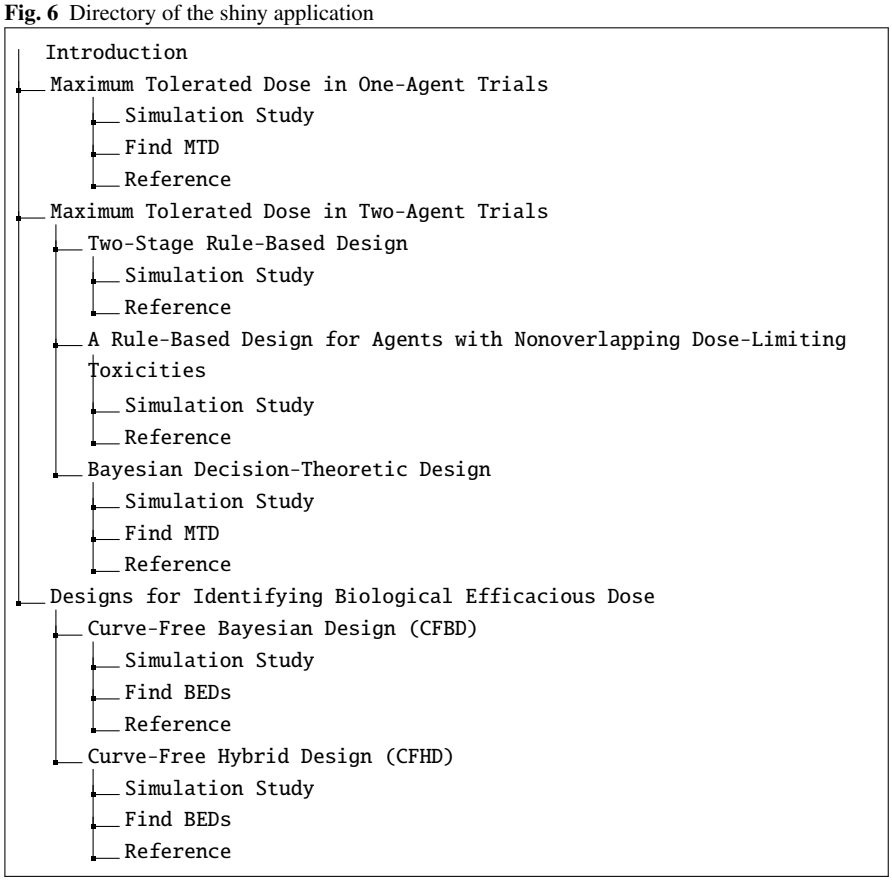
This CFBD design was published [14]. We defer the examples and simulation results of CFBD and CFHD in Section 5.

5 R Packages and Web Application

To help users better understand and utilize our proposed designs, we developed an interactive web application, "Curve-Free Designs", which computes and returns the exact operating characteristics of the designs under user-defined scenarios. The

application is developed using the Shiny package in the R programming language. It has a graphical user interface (GUI), requires no prior programming skills, and is free to access and use on any device that can open an Internet browser. Figure 5 shows the structure of the web application.

Fig. 6 Directory of the shiny application



The web application can be accessed directly using the following URL: https://cisd-stanford.shinyapps.io/CurveFreeDesigns/. Or one can download the source code from Github: https://github.com/CISD-Stanford/CurveFreeDesigns. To install and run the web application from your local machine,

Install Web Application on your local machine

1. Download the .zip file for the web application using the "Download ZIP" button.
2. Unzip the file to any direction of your choice.
3. Open R/Rstudio and run the following code:

```
setwd("directory path of your .zip file")
runApp("Curve-Free_Designs")
```

5.1 Using the application

The application has a simple graphical user interface (GUI), where users set parameters for simulation studies and input data for MTD finding. In simulation study, users need to choose the corresponding simulations, specify scenario parameters and hyperparameters to control the set-up of the trial. For model-assisted designs, we developed three types of simulations to test design robustness: simulation study, sensitivity analysis by random error, and sensitivity analysis by fixed error. In the "Simulation study", the prior means will be set as the same as the true DLT probabilities. For the rest of them, one involves random errors and the other involves fixed errors in prior specifications. In the "Sensitivity analysis by random error", we set $\mu^0_{T,i} = (1 \pm \epsilon_{T,i}) \times P_i$, where $\epsilon_{T,i}$ follow uniform distribution with boundaries 0% and 50% of the corresponding true rates. Here, we choose 50% as the upper boundary of random errors. One can also specify another upper boundary in the Web Application. In "Sensitivity analysis by fixed error", users need to set the fixed error of each dose level just as they set the true DLT probabilities. The scenario parameters to be specified contain the number of dose levels of each agent, the true probabilities of DLT for each dose, the target toxicity rate, etc. Changing the number of dose levels will automatically change the size of the input bar that specifies true DLT probabilities. The hyperparameters include the effective sample size in the beta prior distribution, the magnitude of penalty/reward in the utility function, and minimum probability to conclude, etc. Once the required parameters are set, you can initiate the computations and view the results by clicking on the ***Get operating characteristics*** button. The results will be displayed in a new tab that includes the scenario used in the current setting, along with tabulated operating characteristics and informative plots. Table 4 summarizes all the parameters to be specified in each design.
We also created a feature for the model-assisted designs called "Find MTD" that concludes the MTD based on the current data at each dose level. Please refer to paragraph 5.1 for how to use it.

Curve-Free Bayesian Adaptive (CBA) Design

On the Web Application's second page, you can conduct simulation studies and MTD findings for CBA. This page offers three sub-tabs: "Simulation Study", "Find MTD", and "Reference". To conduct a simulation study, select the type of simulation you want to perform and then specify the true DLT probabilities. If sensitivity analysis is selected, an additional input bar will appear on the right of the true

DLT probabilities input bar. The user can choose the size of the errors or use the default value. Once finished, the remaining parameters to be specified are: target toxicity rate θ_{T}, Maximum acceptable toxicity rate θ_{max}, Minimum sample size n_{min}, Maximum sample size n_{max}, Total number of simulations, and Random seed. Once all parameters are entered correctly, click the button ***Get operating characteristics*** at the bottom, and the results will be generated in a new output tab. For MTD finding, users need to enter the prior mean of DLT probabilities, the number of DLT outcomes and patients enrolled at each dose level, and the current dose level (optional). Once all data are entered appropriately, click the button ***Find MTD/BEDs***, then a table and a plot will be generated in the sidebar on the right. They can also enter the current dose level, but it's optional. If it is entered, the application will evaluate each stopping rule and provide a final decision about whether to stop the trial.

Data-Driven 2+1+3 Design

The third page of the web application contains three designs, among which the first one is the Data-Driven 2+1+3 Design. In this subsection, we are going to explain how to use it. First, users need to choose between Two-Stage Design and Three-Stage Design. The only difference between them is that a stage of searching for a starting combination using DLT and pre-DLT toxicity responses is added before Stage 1 as Stage 0. Once finished, users need to set the values of the lower bound of DLT level θ_{min}, the upper bound of DLT level θ_{max}, true DLT probabilities at each dose level, the number of simulations and random seed. Then, after clicking the button ***Get operating characteristics***, a new output tab containing the results will pop up.

Safety-Driven A+B+C Design

The second one on the third page of the web application is the Safety-Driven A+B+C Design. To get the simulation results, users need to choose the type of A+B+C design first. The available choices in the selection bar are 2+1+3, 4+3+2, 4+4+4, and 2+1+3/4+4+4. In the selection bar, people can choose multiple choices at once to compare their operating characteristics. Then, after setting the true DLT probabilities at each dose level, the number of simulations, and random seed, people also need to set the conditional probabilities of observing only DLT1 and only DLT2, given that at least one DLT occurs and that DLT3 is absent. A set of default values are provided. Once finished, click the button ***Get operating characteristics*** at the bottom, the results will be generated in a new output tab.

The rest of the proposed designs are Curve-Free Bayesian Adaptive (CBA) for two agents, Curve-Free Bayesian Design (CFBD), and Curve-Free Hybrid Design (CFHD). The way of using them is similar to that of CBA (5.1) above. The only difference is that users need to set the true DLT probabilities in a two-dimensional matrix, and users can also customize the magnitude of the penalty defined in the

utility function and the value of the threshold defined in the stopping rule. For a detailed explanation of them, please refer to the section 3.3.2 and section 3.3.3. The difference between CFBD/CFHD and CBA is that, in addition to the true DLT probabilities specification, users also need to specify the true efficacy probabilities. Besides, people can also choose whether to enroll confirmation cohort in the section for CFHD.

5.2 Examples: Simulation Studies for CFBD and CFHD

To help users understand how to use the Web Application, we create an example that examines the operating characteristics of the CFBD and CFHD under six toxicity and efficacy scenarios, each of which provides a variety of dose-efficacy curves: monotone increasing (scenarios 1 and 6), unimodal (scenarios 2 and 3), and increasing with a plateau (scenarios 4 and 5). Table 5 summarizes the true toxicity probability and efficacy probability at each dose level with the BEDs highlighted in boldface type. To study the robustness of CFBD and CFHD, we not only conducted simulation studies but also sensitivity analyses, which are explained in detail in the following sections. We run 5000 trials under each scenario, in which the maximum acceptable DLT probability, θ_{max}, and the minimum acceptable efficacy rate, e_{min}, were both 0.3. The stopping rules for the simulation are given as follows. To prevent incorrect early termination due to misspecified prior distributions, a trial should not be stopped when the sample size is relatively small. Since it takes about 12 patients to have a power of .70 and significance level of .10 to test the hypothesis $H_0 : P_i^E = \pi_E = 0.3$ against $H_1 : P_i^E = 0.1$, with 5 doses in our simulated trials, we set the minimum sample size to stop a trial early as $n_{min} = 5 * 12 = 60$. To account for the sample size constraint of actual phase Ib trials, we limited the maximum sample size to $n_{max} = 100$. Finally, the threshold q defined in the stopping rule is set to 0.90. Users can choose the type of simulation by clicking the selection bar on the left-hand side of the shiny page to choose either option from "Simulation study", "Sensitivity analysis by random error", or "Sensitivity analysis by fixed error". In the current trial setting, users only need to enter either scenario described in Table 5 into the matrix input bar at the bottom of the first section, "Scenario Parameter Set-up", of either CFBD or CFHB, which will be shown after clicking the directory "Designs for Identifying Biological Efficacious Dose". In the next step, enter the hyperparameters into the corresponding input bar or slider bar in the second section. Once finished, after clicking either button at the very bottom, a new tab containing the simulation results will pop up. We created two buttons named "Get Operating Characteristics" and "Compare with CFHD/CFBD". The first button is used to generate the simulation results for CFBD/CFHD only, and the second button is used to compare either CFBD or CFHD to the other one. We also created a check box that enables users to choose whether to enroll confirmation cohort and the size of the confirmation cohort in CFHD. Please note that when the button "Compare CFHD/CFBD" is clicked, without enroll confirmation cohort will be set as default.

5.2.1 Simulation results

The random seed we choose in this example is 1042. That is, the simulation results can be replicated accurately if users select the same random seed. More specifically, the random seed is a starting point for generating the same sequence of random numbers, which ensures that the simulation results remain consistent. The simulation results are summarized in Table 6 and Table 7. The Table 6 contains following summary statistics: (1) the percentage of trials that recommend BEDs (% found); (2) the percentage of trials that gave a good recommendation (% correct), which is defined as the percentage of trials in which all doses in the recommended interval are BEDs; (3) the percentage of in-trial toxicities (% tox); (4) the percentage of in-trial efficacies (% eff) and (5) the average sample size over the 5000 simulated trials ($\bar{n}$). Further details are provided in Table 7.

Finally, we compare CFBD to CFHD to investigate the influence of prior information. In scenario 1, where there is no BED, the two designs performed comparably. In all other scenarios, the average sample sizes are comparable but CFBD has a significantly higher percentage of trials that provided a good recommendation; specifically, the percentage under CFBD is 10–20% higher. Furthermore, as seen in Table 7, the percentage of patients treated at BEDs under CFBD is higher than that under CFHD in all six scenarios. This demonstrates the benefit of incorporating (reliable) prior information, one of the defining features of Bayesian inference.

5.2.2 Sensitivity analysis

To investigate the robustness of CFBD, we also conducted two different types of simulations, one involving random errors and the other involving fixed errors in prior specifications. In the first set of simulations, random errors were added to the means of the Beta prior distributions, which were originally chosen to be equal to the true rates. Specifically, we set $\mu^0_{T,i} = (1 \pm \epsilon_{T,i}) \times P_i$ and $\mu^0_{E,i} = (1 \pm \epsilon_{E,i}) \times P^E_E$, where $\epsilon_{T,i}$ and $\epsilon_{E,i}$ follow uniform distribution with boundaries 0 and 50% of the corresponding true rates. Here, we choose 50% as the upper boundary of random errors. One can also specify another upper boundary in the Web Application. All other settings were the same as described in the previous section. Table 9 summarizes the results, from which we see that CFBD is extremely robust: the operating characteristic of CFBD under misspecifications of parameter values, with random errors up to 50% of the true values, is nearly identical to that without misspecification. We attribute this robustness to sufficient sample size, relatively weak prior information, and the curve-free design.

To study the robustness of CFBD in any specified misspecifications, we added a set of fixed errors to the toxicity probabilities such that the prior MTD is different from the true MTD. In addition, the efficacy probabilities were also modified such that the prior set of BEDs and the true set of BEDs are dismatched (Table 8). All other settings remained the same as described in the previous section. The results are summarized in Table 9. Although the priors were very different from the true

scenario, and the prior MTD and BEDs were completely different from the actual values, CFBD still performed reasonably well.

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Table 4 Parameters to be specified in each proposed design

Symbol	Explanation
Common parameters	
Random Seed	A number used to initialize a pseudorandom number generator.
Total number of simulations	The number of times the algorithm is repeatedly performed
Curve-Free Bayesian Adaptive	
k	The number of dose levels
P_i	True DLT probability of dose level i
θ_{T}	Target DLT probability
θ_{max}	Maximum acceptable DLT probability
n_{min}	Minimum sample size
n_{max}	Maximum sample size
Data-Driven 2+1+3 Design	
I	The number of doses for agent 1
J	The number of doses for agent 2
$P_{i,j}$	True DLT probability of dose combination (i,j)
θ_{min}	The lower bound of DLT probability
θ_{max}	The upper bound of DLT probability
Safety-Driven A+B+C Design	
I	The number of doses for agent 1
J	The number of doses for agent 2
$P_{i,j}$	True DLT probability of dose combination (i,j)
$P(A\|B)$	The conditional probability of observing only DLT1 and only DLT2, given that at least one DLT occurs and that DLT3 is absent
2-dimensional Curve-Free Bayesian Adaptive	
I	The number of doses for agent 1
J	The number of doses for agent 2
$P_{i,j}$	True DLT probability of dose combination (i,j)
θ_{T}	Target DLT probability
α_0	Penalty term in the utility function for $p \leq \theta_{\mathrm{T}}$
η_0	Penalty term in the utility function for $p > \theta_{\mathrm{T}}$
n_{min}	Minimum sample size
n_{max}	Maximum sample size
r_1	Minimum probability to conclude that all doses are evidently too toxic
r_2	Minimum probability to conclude that the current recommended dose is likely to be the MTD
Curve-Free Bayesian Design	
k	The number of dose levels
P_i	True DLT probability of dose level i
P_i^E	True efficacy probability of dose level i
θ_{T}	Target DLT probability
θ_{max}	Maximum acceptable DLT probability
E_{min}	Minimum acceptable efficacy probability
q	The threshold defined in the stopping rule
$n_{min.mtd}$	Minimum sample size for stage 1
$n_{max.mtd}$	Maximum sample size for stage 1
n_{min}	Minimum sample size for stage 2
n_{max}	Maximum sample size for stage 2
n_c	Size of confirmation cohort
Curve-Free Hybrid Design	
k	The number of dose levels
P_i	True DLT probability of dose level i
P_i^E	True efficacy probability of dose level i
θ_{T}	Target DLT probability
θ_{max}	Maximum acceptable DLT probability
E_{min}	Minimum acceptable efficacy probability
q	The threshold defined in the stopping rule
$n_{min.mtd}$	Minimum sample size for stage 1
$n_{max.mtd}$	Maximum sample size for stage 1
n_{min}	Minimum sample size for stage 2
n_{max}	Maximum sample size for stage 2
n_c	Size of confirmation cohort (if confirmation cohort is enrolled)

Table 5 Six scenarios with its shape of efficacy curve; doses in bolds are BEDs

		Dose level				
Scenario		1	2	3	4	5
1	toxicity	0.1	0.2	0.3	0.4	0.5
Increasing	efficacy	0.05	0.1	0.18	0.25	0.3
2	toxicity	0.01	0.05	0.09	0.15	0.2
Unimodal	efficacy	0.1	**0.3**	**0.4**	0.2	0.05
3	toxicity	0.02	0.06	0.12	0.3	0.5
Unimodal	efficacy	**0.3**	**0.4**	0.2	0.1	0.05
4	toxicity	0.02	0.06	0.12	0.3	0.5
Plateau	efficacy	0.1	**0.3**	**0.3**	**0.3**	0.3
5	toxicity	0.1	0.2	0.25	0.4	0.5
Plateau	efficacy	0.2	**0.4**	**0.4**	0.4	0.4
6	toxicity	0.05	0.1	0.2	0.35	0.5
Increasing	efficacy	0.05	0.2	**0.3**	0.4	0.5

Table 6 The average sample size ($\bar{n}$), the percentage of trials that identify at least one BED (% found), the percentage of trials that provided a good recommendation (% correct), and the percentages of toxicity (% tox) and efficacy (% eff) under the proposed Bayesian design (CFBD) and CFBD with the second stage replaced by a frequentist version (CFHD).

Design	$\bar{n}$	% found	% correct	%tox	% eff
Scenario 1: increasing efficacy curve, no BEDs					
CFBD	67.76	6.90	0.00	20.40	11.20
CFHD	76.97	2.60	0.00	20.30	11.20
Scenario 2: unimodal efficacy curve, two BEDs in middle					
CFBD	90.21	98.20	95.60	10.50	26.10
CFHD	83.30	92.30	86.60	10.20	22.90
Scenario 3: unimodal efficacy curve, two BEDs in front					
CFBD	89.43	99.3	97.10	9.10	29.00
CFHD	82.53	93.1	88.30	10.60	27.00
Scenario 4: step efficacy curve, three BEDs in middle					
CFBD	99.24	95.50	96.00	13.80	27.50
CFHD	90.94	79.80	98.50	13.60	26.40
Scenario 5: step efficacy curve, two BEDs in middle					
CFBD	82.98	94.10	90.60	20.00	34.70
CFHD	75.14	91.70	78.40	19.30	33.40
Scenario 6: increasing efficacy curve, one BED in middle					
CFBD	91.71	76.60	45.10	17.90	25.70
CFHD	89.08	60.80	42.10	16.60	23.90

Table 7 The MTD, BED interval $[L^*, U^*]$ selection percentages, and patient allocation percentages for all doses under CFBD(CFHD); correct percentages are in bold

Dose level	1	2	3	4	5
Scenario 1: increasing efficacy curve, no BEDs					
% of MTD	6.2(6.1)	48.2(48.6)	**40.2(39.5)**	5.4(5.8)	0.0(0.0)
% of L^*	3.9(0.0)	0.5(0.1)	1.6(1.5)	0.9(1.0)	0.0(0.0)
% of U^*	3.9(0.0)	0.5(0.1)	1.6(1.4)	0.9(1.1)	0.0(0.0)
% of patients	32.2(34.1)	40.0(36.8)	20.5(22.3)	6.9(6.3)	0.5(0.5)
Scenario 2: unimodal efficacy curve, two BEDs in middle					
% of MTD	0.0(0.0)	0.9(0.9)	9.2(8.3)	32.3(30.2)	**57.7(60.6)**
% of L^*	1.2(1.2)	**23.1(47.9)**	**72.2(42.3)**	1.7(0.9)	0.0(0.0)
% of U^*	1.2(0.1)	**10.1(8.5)**	**83.9(72.4)**	3.0(11.3)	0.0(0.0)
% of patients	6.7(14.4)	**24.2(22.4)**	**32.8(23.7)**	21.7(21.5)	14.5(17.9)
Scenario 3: unimodal efficacy curve, two BEDs in front					
% of MTD	0.1(0.1)	2.4(2.3)	26.9(25.6)	**68.6(70.2)**	2.1(1.9)
% of L^*	**26.3(46.6)**	**71.3(45.6)**	1.1(0.9)	0.6(0.0)	0.0(0.0)
% of U^*	**8.6(6.2)**	**87.8(76.0)**	2.3(10.8)	0.6(0.1)	0.0(0.0)
% of patients	**28.3(27.8)**	**36.6(28.8)**	24.9(28.1)	8.7(13.7)	1.5(1.6)
Scenario 4: step efficacy curve, three BEDs in middle					
% of MTD	0.2(0.3)	2.5(2.0)	24.3(25.2)	**72.0(71.3)**	1.0(1.3)
% of L^*	3.6(0.7)	**40.0(44.2)**	**34.0(24.2)**	**17.8(10.6)**	0.1(0.1)
% of U^*	3.6(0.1)	**31.0(19.3)**	**35.3(30.7)**	**25.4(29.1)**	0.2(0.5)
% of patients	12.9(18.2)	**27.7(25.3)**	**34.5(31.5)**	**23.4(23.2)**	1.5(1.7)
Scenario 5: step efficacy curve, two BEDs in middle					
% of MTD	5.9(5.3)	38.8(37.9)	**45.0(43.9)**	10.3(12.9)	0.0(0.0)
% of L^*	2.5(10.3)	**74.6(73.6)**	**15.1(7.0)**	1.8(0.7)	0.0(0.0)
% of U^*	1.1(0.3)	**50.7(41.3)**	**35.8(39.4)**	6.5(10.7)	0.0(0.0)
% of patients	26.9(33.5)	**40.4(36.8)**	**25.5(22.6)**	6.7(6.6)	0.4(0.5)
Scenario 6: increasing efficacy curve, one BED in middle					
% of MTD	0.8(0.7)	9.4(8.1)	**58.5(57.8)**	31.2(33.0)	0.2(0.0)
% of L^*	7.2(0.0)	7.5(9.3)	**40.2(38.1)**	21.6(13.3)	0.1(0.0)
% of U^*	7.2(0.0)	6.9(3.6)	**35.0(28.3)**	27.3(28.6)	0.2(0.3)
% of patients	12.3(18.0)	31.1(31.4)	**39.4(36.1)**	16.4(13.8)	0.8(0.8)

Table 8 Sensitivity analysis: fixed error priors with incorrect BED sets (disjoint with the true BED sets) ; BED percentages are in bold

Dose level	1	2	3	4	5	Dose level	1	2	3	4	5
Scenario 1: no BEDs becomes one BED						Scenario 4: BED set $\{2, 3, 4\}$ becomes $\{1\}$					
True toxicity	0.1	0.2	0.3	0.4	0.5	True toxicity	0.02	0.06	0.12	0.3	0.5
True efficacy	0.05	0.1	0.18	0.25	0.3	True efficacy	0.1	**0.3**	**0.3**	**0.3**	0.3
Prior toxicity	0.05	0.1	0.2	0.3	0.4	Prior toxicity	0.12	0.35	0.5	0.55	0.6
Prior efficacy	0.1	0.18	0.25	**0.3**	0.4	Prior efficacy	**0.3**	0.3	0.3	0.3	0.1
Scenario 2: BED set $\{2, 3\}$ becomes $\{4\}$						Scenario 5: BED set $\{2, 3\}$ becomes $\{4\}$					
True toxicity	0.01	0.05	0.09	0.15	0.2	True toxicity	0.1	0.2	0.25	0.4	0.5
True efficacy	0.1	**0.3**	**0.4**	0.2	0.05	True efficacy	0.2	**0.4**	**0.4**	0.4	0.4
Prior toxicity	0.09	0.15	0.2	0.3	0.4	Prior toxicity	0.05	0.1	0.2	0.25	0.4
Prior efficacy	0.05	0.1	0.2	**0.3**	0.4	Prior efficacy	0.2	0.2	0.2	**0.4**	0.4
Scenario 3: BED set $\{1, 2\}$ becomes $\{3\}$						Scenario 6: BED set $\{3\}$ becomes $\{2\}$					
True toxicity	0.02	0.06	0.12	0.3	0.5	True toxicity	0.05	0.1	0.2	0.35	0.5
True efficacy	**0.3**	**0.4**	0.2	0.1	0.05	True efficacy	0.05	0.2	**0.3**	0.4	0.5
Prior toxicity	0.06	0.12	0.3	0.5	0.6	Prior toxicity	0.1	0.2	0.35	0.5	0.55
Prior efficacy	0.05	0.1	**0.3**	0.4	0.2	Prior efficacy	0.2	**0.3**	0.4	0.5	0.55

Table 9 Sensitivity analysis: average sample size $\bar{n}$, percentages of any (%found) BED interval and good (%correct) selection, and percentages of toxicity (%tox) and efficacy (%eff) outcomes under correct priors, incorrect priors with random errors and with fixed errors; correct percentages are in bold

Prior type	$\bar{n}$	%found	%correct	%tox	%eff
Scenario 1: increasing efficacy curve, no BEDs					
Correct priors	67.76	6.90	0.00	20.40	11.20
Random error priors	73.23	13.00	0.00	24.00	13.5
Fixed error priors	71.23	10.20	0.00	22.7	12.7
Scenario 2: unimodal efficacy curve, two BEDs in middle					
Correct priors	90.21	98.20	95.60	10.50	26.10
Random error priors	88.46	98.40	96.10	9.70	28.30
Fixed error priors	89.54	98.10	96.40	9.00	27.00
Scenario 3: unimodal efficacy curve, two BEDs in front					
Correct priors	89.43	99.30	97.10	9.10	29.00
Random error priors	88.52	98.70	96.30	11.30	28.50
Fixed error priors	88.86	99.50	97.80	7.90	29.90
Scenario 4: step efficacy curve, three BEDs in middle					
Correct priors	99.24	95.50	96.00	13.80	27.50
Random error priors	98.89	93.70	94.90	13.30	27.10
Fixed error priors	98.48	88.20	95.70	8.30	25.60
Scenario 5: step efficacy curve, two BEDs in middle					
Correct priors	82.98	94.10	90.60	20.00	34.70
Random error priors	81.26	85.70	93.80	18.10	32.80
Fixed error priors	84.12	97.90	84.90	22.40	35.90
Scenario 6: increasing efficacy curve, one BED in middle					
Correct priors	91.71	76.60	45.10	17.90	25.70
Random error priors	90.87	68.80	48.50	16.40	24.20
Fixed error priors	90.05	61.80	54.90	14.70	22.40