The i3+3 Design for Phase I Clinical Trials

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Abstract

Purpose The 3+3 design has been shown to be less likely to achieve the objectives of phase I dose-finding trials when compared with more advanced model-based designs. One major criticism of the 3+3 design is that it is based on simple rules, does not depend on statistical models for inference, and leads to unsafe and unreliable operating characteristics. On the other hand, being rule-based allows 3+3 to be easily understood and implemented in practice, making it the first choice among clinicians. Is it possible to have a rule-based design with great performance?

Methods We propose a new rule-based design called i3+3, where the letter "i" represents the word "interval". The i3+3 design is based on simple but more advanced rules that account for the variabilities in the observed data. We compare the operating characteristics for the proposed i3+3 design with other popular phase I designs by simulation.

Results The i3+3 design is far superior than the 3+3 design in trial safety and the ability to identify the true MTD. Compared with model-based phase I designs, i3+3 also demonstrates comparable performances. In other words, the i3+3 design possesses both the simplicity and transparency of the rule-based approaches, and the superior operating characteristics seen in model-based approaches. An online R Shiny tool (https://i3design.shinyapps.io/i3plus3/) is provided to illustrate the i3+3 design, although in practice it requires no software to design or conduct a dose-finding trial.

Conclusion The i3+3 design could be a practice-altering method for the clinical community.

1 INTRODUCTION

1.1. Background

Phase I dose-finding trials represent the first stage of testing a new drug or new therapy in humans and are crucial in clinical drug development as they provide dose recommendation for later phase clinical trials. The primary goal of phase I trials is to assess dose limiting toxicities (DLT) and find the maximum tolerated dose (MTD) while maintaining patient safety. Statistical designs for phase I dose-finding trials can be generally divided into two classes: rule-based methods and model-based methods. The most widely used 3+3 design (1) is an example of rule-based methods, in which dose escalation and de-escalation decisions are based on a set of prespecified rules. It is by far the most popular method in practice due to its simplicity.

Clinicians and drug developers only need to follow a set of rules (2) to design and conduct the dose-finding trials without needing to understand statistical models or run computer programs. The other class of designs uses parametric or nonparametric statistical models to describe the underlying mechanism of observed dose-toxicity relationship. Statistical inference based on the models leads to desirable decisions for dose allocation, typically optimized according to a certain criterion. The continuous reassessment method (CRM) by O' Quigley et al. (3) is an example of model-based designs. In practice, the CRM design often requires expertise in statistical modeling and the ability to execute computer programs for real-trial applications.

In addition to the classical model-based designs like CRM, there is an increasing interest in a type of model-based designs, called interval-based designs that demonstrate comparable operating characteristics to the classical model-based designs but with simpler implementation like the rule-based designs. Some notable examples include the mTPI (4) and mTPI-2 designs (5), the cumulative cohort design (CCD) (6) and the Bayesian optimal interval design (BOIN) (7). One important advantage of these designs is that the decisions of dose allocation can be pretabulated in advance, making the decision process transparent and intuitive to clinicians. However, they all rely on underlying models and inference that require expertise in statistics and mathematics.

1.2. A motivating example

The proposed i3+3 design is motivated by a debatable decision based on the mTPI design (5). We first provide a brief review of the mTPI design to set the stage for the upcoming discussion. The mTPI design requires investigators to provide two input values, the target probability of

toxicity p_T and the equivalence interval (EI), defined mathematically as $[p_T - \varepsilon_1, p_T + \varepsilon_2]$. The target probability of toxicity p_T specifies the highest toxicity rate of the MTD (e.g., p_T =0.3) and the EI provides a range around the target probability so that doses with toxicity probabilities inside the EI will also be considered as the MTD. For example, when p_T =0.3 and EI is [0.25, 0.35], the target toxicity rate of the MTD is 0.3, but a dose with toxicity rate between 0.25 and 0.35 will also be considered as the MTD. The use of EI allows some variabilities in the statistical inference and flexibility for real-world clinical trials.

Statistically, mTPI uses an optimal decision rule for assigning patients (4). However, some decisions of mTPI, even though optimal and accounting for the data variability, may be considered risky in clinical practice. For example, suppose in a dose-finding trial, the target toxicity probability is $p_T = 0.3$ and the EI is [0.25, 0.35]. This means that the MTD should have a toxicity probability near 0.3 but not below 0.25 or above 0.35. Suppose 6 patients have been enrolled at a dose and 3 of them experience DLTs at a dose currently being used for treatment. Based on the observed data, a trial design needs to provide a decision to select the dose level at which the next cohort of patients will be assigned. The decision of the mTPI design is "S", to stay and enroll more patients at the current dose. The decision "S" can be deemed too aggressive since the observed toxicity rate is 3/6 = 0.5, which is higher than the target rate $p_T = 0.3$. In practice, the decision "D", to de-escalate the dose level is considered to be safer and more desirable. Through personal communication, this type of argument has been raised by IRB review committees and regulatory agencies. However, a question one may ask is that why a mathematically optimal decision rule in mTPI produces the decision "S" that is perceived too risky in practice?

To address this question, we begin by noting that there is no consensus on what decisions are acceptable in real-world trials. Oftentimes, whether a decision is acceptable depends on the review committee's experiences, preference, and common sense. For example, if 3 out of 3 patients experience DLTs at a dose, the only acceptable decision is "D", to de-escalate the dose level regardless of what statistical design is used. However, it is less obvious which decisions are acceptable when 3 out of 6 patients have DLTs in a trial with a target toxicity rate p_T =0.3 and EI = [0.25, 0.35]. So why is decision "S" considered not acceptable by review committees here? The most obvious answer would be that the observed toxicity rate 3/6=0.5 is higher than the target rate 0.3. An observed toxicity rate higher than the MTD target rate raises safety concern of the dose, and therefore the decision "S", which allows more patients to be treated at the same dose, may be considered too risky in practice. However, this may not be the only reason. Let us consider another example. The same decision "S" is used by the 3+3 design if 1 out of 3 patients experiences DLT at a dose. The 3+3 design defines the MTD as the highest dose with no more than 1 out of 6 patients experiencing DLT. In other words, the target toxicity rate of the 3+3 design is about 1/6. When 1 out of 3 patients experiences DLT, the observed toxicity rate is 1/3, which is higher than 1/6, and yet the decision "S" under the 3+3 design is widely accepted in practice. So why is decision "S" acceptable when 1 out of 3 patients experiences DLT with a target rate 1/6 but not acceptable when 3 out of 6 patients have DLTs with a target rate 0.3?

The answer lies in the difference of the sample sizes (and associated data variabilities) of the observed data, 6 patients versus 3 patients, between the two examples. Consider the 3+3 case where "S" is acceptable when 1 out of 3 patients has DLT and the target rate is 1/6. Even though

the observed toxicity rate 1/3 is twice higher than the target rate 1/6, there is only 3 patients worth of information, which does not sufficiently distinguish 1/3 from 1/6. For example, with 1 fewer DLT, the observed rate would be 0/3, way below 1/6. In contrast, in the second case where 3 out of 6 patients have DLT and the target rate is 0.3, not only is the empirical rate 3/6 higher than the target rate, but even if 1 fewer patient were to have DLT, the observed rate would be 2/6 which would still be higher than 0.3. Therefore, the observed rate 3/6 in the second case is more informative than the observed rate 1/3 in the first case, despite both observed rates being higher than the target rates. As a result, the decision "S" is considered not acceptable in the case of 6 patients but acceptable in the case of 3 patients.

Motivated by this reasoning, we propose a new rule-based design, the i3+3 design in which the letter "i" stands for "interval". The main innovation of i3+3 is to add an additional criterion into the 3+3 like rules so that data variability is accounted for. The new criterion considers the gap between two possible data points and its relative magnitude to the EI.

2 The PROPOSED i3+3 DESIGN

2.1.Dose-finding algorithm

Suppose a set of d = 1, ... D ascending doses is tested in a trial. Assume the target toxicity rate p_T for the MTD (e.g., $p_T = 0.3$) and the EI (e.g., EI = [0.25, 0.35]), have been specified and fixed for the trial. Suppose dose d is the dose currently used to treat patients, n is the number of patients who have been treated at dose d, and x is the number of patients who have experienced DLTs at dose d. Assume patients are enrolled and assigned to doses in cohorts. That is, the next cohort of patients may not be enrolled until toxicity outcomes from the previous cohorts of

enrolled patients have been fully observed. Given the observed data, the i3+3 design identifies an appropriate dose for the next cohort of patients. We propose a set of rules in Table 1 that fulfills the task. Specifically, these rules compare two quantities, $\frac{x}{n}$ and $\frac{x-1}{n}$, to the EI, and depending on the comparison outcome, decide the next dose level for enrolling patients.

In words, the i3+3 design can be summarized as follows: at the current dose d, calculate two quantities $\frac{x}{n}$ and $\frac{x-1}{n}$.

- If $\frac{x}{n}$ is below the EI, escalate ("E") and enroll patients at the next higher dose ($(\underline{d+1})$;
 - o else, if $\frac{x}{n}$ is inside the EI, stay ("S") and continue to enroll patients at the current dose \underline{d} ;
 - else, if $\frac{x}{n}$ is above the EI, there are two scenarios:
 - 1) if $\frac{x-1}{n}$ is below the EI, stay ("S") and continue to enroll patients at the current dose \underline{d} ,
 - 2) else, de-escalate ("D") and enroll patients at the next lower dose (d-1).

When *d* is the highest dose or the lowest dose, the above rules need to be modified as special cases.

- 1. If the current dose is the highest dose, and $\frac{x}{n}$ is below the EI, stay ("S") instead of escalating ("E") and continue to enroll patients at the current dose. This is because there is no dose to escalate to.
- 2. If the current dose is the lowest dose, and $\frac{x}{n}$ is above the EI, stay ("S") instead of potentially de-escalating ("D") and continue to enroll patients at the current dose. This is because

there is no dose to de-escalate to.

Following the mTPI and mTPI-2 designs, we add two safety rules as ethical constraints to avoid excessive toxicity:

- Safety rule 1 (<u>early termination</u>): Suppose that dose 1 has been used to treat patients. If $Pr(p_1>p_T|x_1,n_1)>\xi$ for $\xi=0.95$, terminate the trial due to excessive toxicity.
- Safety rule 2 (dose exclusion): Suppose that the decision is to escalate from dose d to (d+1). If $Pr(p_{d+1}>p_T|x_{d+1},n_{d+1})>\xi$ for $\xi=0.95$, then treat the next cohort of patients at dose d instead of (d+1), and dose (d+1) and higher doses will be removed from the trial. These doses will be marked as "DU" to indicate that they are Unacceptable to use in the trial anymore.

Under the i3+3 design, a trial is terminated either when a prespecified sample size is reached or according to Safety rule 1.

2.2. Examples and Software

In Table 2, we provide two cases to illustrate the application of the i3+3 design. In case 1, n = 6 patients are treated at dose d, $p_T = 0.3$ and the EI is [0.25, 0.35]. In case 2, n = 3, $p_T = 0.17$ and the EI is [0.12, 0.22]. We also include the decisions of mTPI and mTPI-2, two intervalbased designs for comparison. In either case, the three designs agree in all decisions except for one. In case 1, the i3+3 decision for x = 3 is "D", to de-escalate to dose (d - 1). With the same setting, the mTPI decision is "S", to continue treating at dose d. This decision is considered too aggressive in practice according to our previous discussion. In case 2, the i3+3 decision for x = 1 is "S", to continue treating at dose d which coincides with the 3+3 design. However, the mTPI-2 decision is "D", to de-escalate to dose (d - 1), which may not be preferred by physicians who

side with the 3+3 design. In both cases, the i3+3 design seems to make the "humanly desirable" decisions as opposed to the model-based designs like mTPI and mTPI-2.

In addition, based on the proposed i3+3 algorithm in Table 1, we can easily generate decisions for any number of n patients, not just restricted to 3 or 6. We provide an R Shiny tool freely available at https://i3design.shinyapps.io/i3plus3/ that generates decision tables based on the i3+3 design for any p_T and EI values. See Figure 1 for an example for a trial with $p_T = 0.3$ and EI =[0.25, 0.35]. In the decision table, we present decisions in terms of three letters, "D", "S", and "E", which correspond treating future patients at dose level (d-1), d, and (d+1), respectively. The letter "U" represents the situations where Safety rule 2 is invoked. This table makes the i3+3 decisions transparent to the investigators prior to trial start and can be used to guide all the dose assignment decisions throughout the trial. Alternatively, investigators can memorize and follow the simple rules in Table 1 to guide dose assignments in the trial, which only requires comparing $\frac{x}{n}$ and $\frac{x-1}{n}$ to the EI. The i3+3 is sufficiently simple and intuitive for this alternative choice.

In addition, the R Shiny tool conducts simulation based on the i3+3 design and allows investigators to examine the operating characteristics of the design, which will be discussed next.

2.3. Estimation of MTD

When a trial is terminated, the MTD selection under the i3+3 design follows the same procedure as in the mTPI and mTPI-2 designs. Specifically, let p_T denote the target toxicity rate, and ϵ_1 , ϵ_2 are small positive constants such that EI= $[p_T - \epsilon_1, p_T + \epsilon_2]$. For example, $\epsilon_1 = \epsilon_2 = 0.05$. Let p_d denote the probability of toxicity at dose d. Assume n_d patients have been treated at dose d, and x_d of them experienced DLTs. Therefore, we assume $x_d | p_d \sim Bin(n_d, p_d)$,

follows a binomial distribution. In addition, assume the prior distribution $p_d \sim$

Beta(0.005,0.005) as in the mTPI and mTPI-2 designs. These parameter values of 0.005 are chosen so that the beta priors have little impact on the posterior distribution, which is given by $p_d|(x_d,n_d) \sim Beta(x_d+0.005,n_d-x_d+0.005)$. Therefore, the posterior mean toxicity probability at dose d is given by

$$\hat{p}_d = \frac{x_d + 0.005}{n_d + 0.01}$$

To impose the monotonicity of the dose-toxicity relationship, isotonic regression is applied to the posterior means \hat{p}_d using the pool adjacent violators algorithm (8). This algorithm replaces adjacent estimates that violate the monotonicity assumption with their weighted average, where the weights are the posterior variance at each dose level. Let \tilde{p}_d be the isotonic-transformed posterior means for all the doses. The estimated MTD is the dose with the smallest difference

$$d^* = \operatorname*{argmin}_{d \in \{1, 2, \dots D\}} |\tilde{p}_d - p_T|$$

among all the doses d for which $n_d>0$ and $\tilde{p}_d\leq$ ($p_T+\epsilon_2$).

If more than one dose of d^* exists, it means there are ties for which the value \tilde{p}_{d^*} is the same. Then we choose MTD according to the following simple rules:

- a) If $\tilde{p}_{d^*} > p_T$, the suggested MTD is the lowest dose in d^* .
- b) If $\tilde{p}_{d^*} \leq p_T$, the suggested MTD is the highest dose in d^* .

3 OPERATING CHARACTERISTICS OF THE i3+3 DESIGN

3.1 Simulation Setup

Via repeated simulation trials, we assess and compare the operating characteristics of the i3+3 design. For comparison, we also include the 3+3, mTPI, mTPI2, BOIN, CRM and the Bayesian Logistic Regression Model (BLRM) (9) designs in the simulation. Simulated trials are generated

based on scenarios that specify the true toxicity rate of each dose. We slightly modified the three sets of 14 scenarios in (10) that assume six doses for a trial and three different target p_T values of 0.1, 0.17, and 0.3, respectively. Scenarios for $p_T = 0.17$ are generated by subtracting 0.03 from the original scenarios for $p_T = 0.2$ in (10). See Appendix A for details. This gives a total of 42 scenarios. A sample size of 30 patients is used for each trial with a cohort size of 3. For the mTPI and mTPI-2 designs, the EI is $[p_T - 0.05, p_T + 0.05]$. For the BOIN design (8), we set $(p_T - \lambda_e) = 0.05$ and $(\lambda_d - p_T) = 0.05$ so that the actual intervals for decision making among BOIN, mTPI and mTPI-2 are identical. For the BLRM design, the EWOC parameter is set at 0.5. A detailed description of the CRM and BLRM used in the simulation study is provided in Appendix B. Under each simulation scenario, we generate 1,000 simulated trials.

3.2 Simulation Results

We characterize the true MTDs as any doses with toxicity probabilities inside the EI. If no doses satisfy the criterion, the true MTD is the highest dose among those with true toxicity probabilities $p_d < p_T$. If no MTD could be identified based on the two criteria, then the particular scenario does not have a true MTD, which means the decision of selecting any dose as the MTD would be wrong.

To assess the performance of a dose-finding design, we consider the following criteria:

- 1. Reliability or the percentage of correct selection (PCS), defined as the percentage of the trials that the MTD is correctly selected. When all the dose levels are above the MTD, PCS is defined as the percentage of early termination of trials.
- 2. Safety, defined as the average percentage of the patients treated at or below the true

MTDs across the simulated trials.

A desirable dose-finding design should demonstrate good balance between patient safety and ability to identify the true MTD. Additional results such as the percentage of trials concluding a dose above the true MTD or percentage of stopping a trial before reaching maximum sample size are given in Appendix C.

To summarize the simulation results, we take pair-wise differences between the i3+3 design and another design under comparison in their safety and reliability values for the same scenario, and display the results through the boxplots in Figure 2. A positive value means the design under comparison is safer or more reliable than the i3+3 design. As can be seen, BLRM with EWOC=0.5 is a safer but ultra-conservative design than i3+3. This has also been observed in the recent work (11). In general, the i3+3 design demonstrates comparable safety performance with mTPI, mTPI-2, BOIN and CRM, and the 3+3 design shows the worst safety among all the designs under comparison. In terms of reliability, the i3+3 design performs similarly with the mTPI, mTPI-2, BOIN and CRM designs, while the BLRM and 3+3 designs are the least reliable in the identification of the true MTDs. Overall, the i3+3 design shows comparable operating characteristics to the main-stream model-based designs. The detailed simulation results are provided in Appendix C.

3.3 Sensitivity Analysis of the EI and Cohort Size

The i3+3 design requires the investigators to specify p_T and EI. Our simulation studies have examined the performance of i3+3 with different p_T values. We now assess the performance of the i3+3 design when the length of EI is varied. In addition, we change the cohort size from 3 to different values since the i3+3 design can be applied to any cohort size values despite the name.

Sensitivity to different EI Table 3 presents the results of the sensitivity analysis. Specifically, we select a sequence of equal-spaced values of ε_1 , ε_2 so that the resulting symmetric EIs range from $(p_T \pm 0 * p_T)$ to $(p_T \pm 0.2 * p_T)$. For each EI value and each of the 14 scenarios with the same p_T , we simulated 1,000 trials with a cohort size of 3 and total sample size of 30. Table 3(a) displays the safety, reliability and percent toxicity (defined as the percentage of patients having DLTs in all of the simulated trials) for different combinations of p_T and EI values. For all three p_T values, safety (the percentage of patients treated at or below the true MTD) and reliability (the probability of identifying the true MTD) tend to increase with the length of EI. The percent toxicity is rarely affected by changing the length of EIs. This is reasonable and a discussion will be provided next.

Sensitivity to different cohort size We fix $p_T = 0.3$ and EI = [0.25, 0.35], and conduct simulations using i3+3 with cohort sizes of 2,3,4,5,6 or a random cohort size within a trial. Since the sample size 4 is not a factor of the total sample size 30, we simulated trials of cohort size 4 with sample size 28 and 32. The results of total sample size 28 are not as good as those with sample size 32. Therefore, we suspect that the larger sample size might have led to better performance. The random value is generated from $\{2,3,4,5\}$ with equal probability and applied to each step of the decision making within a trial. For each cohort size, 1,000 simulated trials are performed. The results are shown in Table 3(b). The performance of the i3+3 design is robust to different cohort sizes.

4 DISCUSSION

The i3+3 design is a simple and intuitive rule-based design demonstrating superior performance than the 3+3 design and similar operating characteristics with the model-based designs. The i3+3 design is versatile since it can accommodate different target p_T values and different cohort sizes. Being a rule-based approach, the i3+3 design can be attractive to clinicians who are used to rule-based designs like 3+3. Other than the slightly different decision tables (Figure A1 in Appendix D), the i3+3, mTPI, and mTPI-2 designs use the same safety rules and same inference to select the MTD. Because the mTPI and mTPI-2 designs have been well established in the literature with desirable performance (4,5,11,12), we decide not to conduct more and larger simulations, such as a simulation study with 1,000 random scenarios (13), to further evaluate the operating characteristics of the i3+3 design. The i3+3 design is expected to perform at a similar level as the mTPI and mTPI-2 designs due to its similar but slightly improved decision table, which puts i3+3 in par with other major model-based designs.

It is interesting that a rule-based design like i3+3 can achieve similar performance as model-based designs. This seems to defy the common statistical belief that model-based inference is superior than rule-based inference. We believe the model-based inference is still superior in general as they offer flexibility and scope for extension. Model-based designs can handle dose-skipping, dose-finding studies with a large number of similar doses, various dose ranges, and more complex patient outcome such as late-onset toxicity. However, in the special case of standard phase I dose-finding trials, due to the ethical constraints to maintain a strict safety control for dosing decisions, model-based inference is heavily restricted by safety rules such as the escalation with over dose control (EWOC, 14) for CRM, the aforementioned Safety rules 1&2 for mTPI, mTPI-2, and BOIN. Bounded by theses practical rules, we believe model-based

inference can be approximated by rule-based inference.

In addition, the reason i3+3 performs well is partly due to the use of two values $\frac{x}{n}$ and $\frac{x-1}{n}$ in the decision rules (see Table 1), instead of just one value $\frac{x}{n}$ as seen in the 3+3 design. Let us define the difference $(\frac{x}{n} - \frac{x-1}{n}) = \frac{1}{n}$ the minimum rate difference (MRD) which measures the smallest difference in the observed toxicity rates based on n patients. As n becomes larger, the MRD becomes smaller, and the variability in the data is smaller. The i3+3 design smartly compares MRD with the length of the EI in order to select between two decisions, de-escalate or stay. It chooses to stay instead of de-escalation when the observed toxicity rate $\frac{x}{n}$ is above the EI and $\frac{x-1}{n}$ is below the EI. This is because the variability of the data is so large that two adjacent data points, $\frac{x}{n}$ and $\frac{x-1}{n}$, reside on either side of the EI, thereby unable to inform whether the true toxicity rate is near or inside the EI. A smart cohort size can be specified based on the comparison between MRD and the EI length. For example, one could choose the cohort size C so that the MRD value $\frac{1}{3xc}$ with 3 cohorts at a dose is lower than the EI length.

The i3+3 design, like mTPI, mTPI-2, BOIN and CCD, uses data on the current dose to make up-and-down decisions for dose finding. This type of up-and-down decisions generates a Markov chain of dose assignments (Ivanova et al., 2007) which borrows information across doses that have been used for treatment. This is in contrast to the explicit information sharing through a dose-response model as seen in the CRM and BLRM designs. Both philosophies can work well if the goal is to identify the MTD in a classical dose-finding trial. One advantage of model-based approaches is the ability to accommodate prior information such as historical data from previous

clinical trials. However, the model-free approach like the i3+3 or model-assisted approaches like mTPI are practically simpler, and offer transparency in the decisions to clinicians.

The i3+3 design only depends on the input of p_T and EI. The target toxicity rate p_T is easily determined as most phase I trials use either 30% or 17%. These two values are results of the popularity of the 3+3 design, which typically targets MTD with toxicity rates in this range. The equivalence interval can be elicited by providing a heuristic boundary around the target p_T . Let us consider an example. Suppose p_T is set at 0.3. This means that if 100 patients were treated at the MTD, about 30 patients would experience DLT. Then the clinician can find a number lower than 30, say 25, so that any number below 25 would warrant an escalation as the dose is deemed lower than the MTD. Similarly, a number above 30, say 35, can be elicited so that any number above 35 would warrant a de-escalation as the dose is deemed higher than the MTD. These two numbers give a rate of 0.25 as the lower bound and 0.35 as the higher bound of the EI. That is, this elicitation gives an EI of [0.25, 0.35]. Changing the two numbers results in different EIs. Through the aforementioned sensitivity analysis, we found that the i3+3 design performs well with a wider EI. This is because a wider EI allows a wider range of doses to be considered as the MTD. However, the EI cannot be too wide to become clinically meaningless. For example, an EI of [0.1, 0.6] is not acceptable since it implies any doses with a toxicity rate between 0.1 and 0.6 can be considered as the MTD. We recommend that the EI is in the range of $(p_T \pm \alpha * p_T)$ for α no more than 20% since a >20% deviation from the target value p_T is usually considered excessive in practice.

Users in practice can modify the decision rules and stopping rules based on specific scenario.

The dose assignment decisions of i3+3 must be used with caution when no more than 3 patients are treated at any dose. For example, when 1 out of 1 patient or 2 patients experienced DLT, the i3+3 design recommend to "Stay", which might be considered too risky. However, in practice it is rare to make a dosing decision after 1 or 2 patients are assigned to a dose. Therefore, users can eliminate the decisions corresponding to 1 or 2 patients if such decisions will never be considered.

Alternative stopping rule, such as stop a trial if more than m number of consecutive patients have been assigned to a dose (e.g., m = 6 or 9 defined by the users), can be considered. This allows early stopping of a trial, although it may lead to premature stopping due to limited sample size.

Lastly, despite the name i3+3, the proposed design can be used with different cohort size other than 3 as demonstrated in the sensitivity analysis. We name the new design i3+3 to highlight the algorithmic nature of the method just like the 3+3 design.

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Table 1: The dose-finding algorithm of the i3+3 design. Notation: 1) d: the current dose that is being tested in the trial; 2) n: the number of patients at the current dose; 3) x: the number of patients with DLTs at the current dose. The target toxicity probability is assumed to be p_T and the equivalence interval is denoted as $[p_T - \varepsilon_1, p_T + \varepsilon_2]$. A value is "below" the EI means that the value is smaller than $(p_T - \varepsilon_1)$, the lower bound of the EI. A value is "inside" the EI means that the value is larger than or equal to $(p_T - \varepsilon_1)$ but smaller than or equal to $(p_T + \varepsilon_2)$. A value is "above" the EI mean that the value is larger than $(p_T + \varepsilon_2)$.

	Current dose: d,	No. enro	lled: n,	No. DLTs: x	
Conditio	n			Nex	ct dose level
$\frac{x}{n}$ below E	I				d+1
$\frac{x}{n}$ inside E	l				d
$\frac{x}{n}$ above E	I and $\frac{x-1}{n}$ below EI				d
$\frac{x}{n}$ above E	I and $\frac{x-1}{n}$ inside EI				d-1
$\frac{x}{n}$ above E	I and $\frac{x-1}{n}$ above EI				d-1

Table 2: Two cases to illustrate the decisions of the i3+3 design in comparison to the mTPI and mTPI-2 designs. In case 1, the target toxicity probability is 0.3, the EI is [0.25, 0.35], and a total of 6 patients are treated at the current dose. In case 2, the target toxicity probability is 0.17, the EI is [0.12, 0.22], and a total of 3 patients are treated at the current dose. Highlighted are where i3+3 is different from mTPI or mTPI-2.

Current dose: d No. enrolled: n =6	_	et probability: $[arepsilon_1, p_T + arepsilon_2] =$	· -
No. DLTs: x		Next dose leve	el
	i3+3	mTPI	mTPI-2
0	d+1	d+1	d+1
1	d + 1	d+1	d+1
2	d	d	d
3	d-1	d	d-1
4	d-1	d-1	d-1
5	d-1	d-1	d-1
6	d-1	d-1	d-1

Case 1

Current dose: d No. enrolled: n =3		t probability: $p_{ au_1}, p_T + \varepsilon_2] =$	
No. DLTs: x		Next dose leve	el .
	i3+3	mTPI	mTPI-2
0	d+1	d+1	d+1
1	d	d	d-1
2	d-1	d-1	d-1
3	d-1	d-1	d-1

Case 2

Table 3. The operating characteristics of the i3+3 design for varying length of EI (a) and cohort size (b). Safety is defined as the fraction of patients treated at or below the true MTD. Reliability is defined as the fraction of trials selecting the true MTD. %Toxicity is defined as the fraction of patients experiencing in all the simulated trials under each row. The subscripts are standard deviations of the mean values across all the scenarios. Each mean value is averaged across all the simulated trials for a given scenario. In (a), each row corresponds to a different combination of p_T and EI, where EI is denoted by $[p_T - \varepsilon_1, p_T + \varepsilon_2]$. We fix sample size at 30 and cohort size 3, and simulate 1,000 trials for each of the 42 scenarios in Appendix A. Each row corresponds to 14 scenarios with the same p_T value. In (b), we set $p_T = 0.3$ and EI= [0.25, 0.35], using the 14 scenarios in Appendix A. Each row corresponds to a different cohort size. Averaged values and the standard deviations of safety, reliability and percent toxicity are listed. Since the cohort size 4

is not a factor of the sample size 30, trials are simulated with both sample size 28 and sample size 30. 4⁻: Trials simulated with cohort size 4 and sample size 28; 4⁺: Trials simulated with cohort size 4 and sample size 32; **: Random cohort size means randomly selecting the cohort size from the set {2,3,4,5} with replacement and equal probability.

p_T	EI	Safety	Reliability	%Toxicity
0.1	0.1	$0.411_{0.286}$	0.436 _{0.232}	$0.111_{0.037}$
	[0.095, 0.105]	$0.411_{0.286}$	$0.439_{0.230}$	$0.111_{0.037}$
	[0.090, 0.110]	$0.479_{0.321}$	$0.489_{0.206}$	$0.111_{0.037}$
	[0.085, 0.115]	$0.470_{0.321}$	$0.502_{0.229}$	$0.111_{0.037}$
	[0.080, 0.120]	$0.503_{0.311}$	$0.549_{0.189}$	$0.107_{0.037}$
0.17	0.17	$0.433_{0.305}$	$0.433_{0.287}$	$0.164_{0.049}$
	[0.1615, 0.1785]	$0.496_{0.309}$	$0.428_{0.273}$	$0.150_{0.046}$
	[0.1530, 0.1870]	$0.537_{0.332}$	$0.465_{0.251}$	$0.150_{0.046}$
	[0.1445, 0.1955]	$0.537_{0.332}$	$0.467_{0.251}$	$0.150_{0.046}$
	[0.1360, 0.2040]	$0.578_{0.344}$	$0.565_{0.234}$	$0.150_{0.046}$
0.3	0.3	$0.579_{0.308}$	$0.476_{0.291}$	$0.246_{0.063}$
	[0.285, 0.315]	$0.613_{0.318}$	$0.507_{0.272}$	$0.246_{0.063}$
	[0.270, 0.330]	$0.614_{0.318}$	$0.548_{0.235}$	$0.246_{0.062}$
	[0.255, 0.345]	$0.649_{0.334}$	$0.609_{0.213}$	$0.245_{0.062}$
	[0.240, 0.360]	$0.731_{0.277}$	$0.674_{0.199}$	$0.243_{0.062}$

(a)

Cohort size	Safety	Reliability	% Toxicity
2	0.733 _{0.254}	0.631 _{0.218}	0.246 _{0.062}
3	0.731 _{0.277}	0.657 _{0.216}	0.243 _{0.062}
4-	0.711 _{0.278}	0.638 _{0.217}	0.251 _{0.060}
4+	0.805 _{0.267}	0.572 _{0.276}	$0.218_{0.071}$
5	0.726 _{0.293}	0.633 _{0.232}	$0.235_{0.072}$
6	0.723 _{0.279}	0.640 _{0.217}	0.244 _{0.062}
Random**	0.743 _{0.275}	0.630 _{0.229}	0.239 _{0.064}

(b)

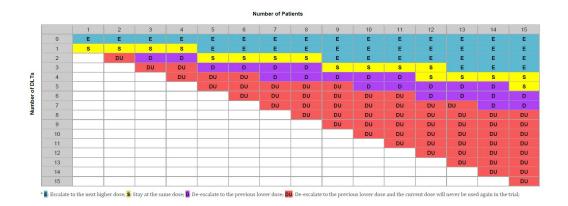
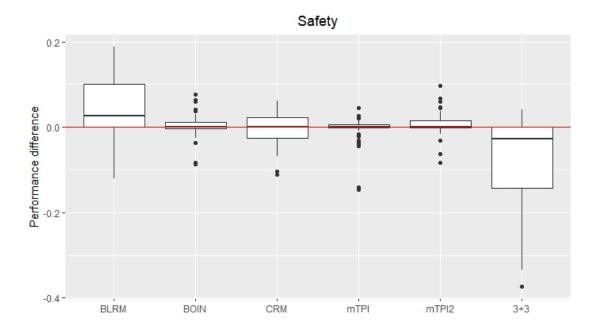


Figure 1: An example of the decision tables for the i3+3 design. For each "Number of Patients" (column), the decisions "D", "S", "E" are listed for each "Number of DLTs" (row). Letter "DU" stands for de-escalating to the previous lower dose, and the current dose is deemed unacceptable according to Safety Rule 2 so that it will never be used again for the rest of the trial. Here, the target toxicity probability $p_T = 0.3$ and EI = [0.25, 0.35].



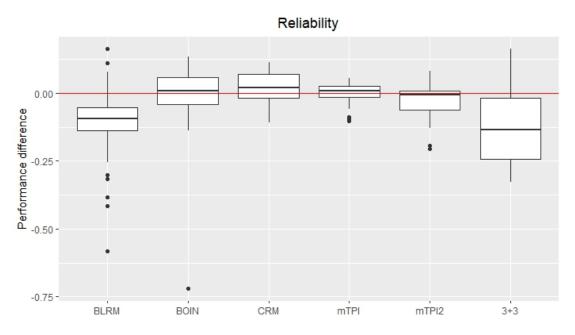


Figure 2: Comparison of *safety* and *reliability*. Six designs (mTPI2, mTPI, BOIN, CRM, BLRM and 3+3) are compared with i3+3. Denote any of the six designs as design X. Upper panel [Safety]: each boxplot describes the differences of the safety values between design X and i3+3 averaged across 42 scenarios. A value greater than zero means design X puts more percentages of patients at the MTD or doses below the MTD than i3+3. Lower panel [Reliability]: each boxplot describes the differences of the reliability values between design X and i3+3 averaged across all 42 scenarios. A value greater than zero means design X is more likely to identify the true MTD than i3+3.

Appendix A **Simulation scenarios**

We adopted the 42 scenarios in Ji and Wang (2013) for $p_T = 0.1$, 0.17, and 0.3, where scenarios for $p_T = 0.17$ were generated by subtracting 0.03 from the original scenarios for $p_T = 0.2$ in Ji and Wang (2013). Each scenario contains six true toxicity probabilities for all the six doses in the simulated clinical trials. They are listed as follows.

$p_T = 0.1$						
Scenarios#	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6
1	0.04	0.05	0.06	0.07	0.08	0.09
2	0.15	0.2	0.25	0.3	0.35	0.4
3	0.01	0.1	0.2	0.25	0.3	0.35
4	0.01	0.02	0.03	0.04	0.1	0.25
5	0.05	0.4	0.5	0.6	0.65	0.7
6	0.01	0.03	0.05	0.4	0.5	0.6
7	0.01	0.02	0.03	0.04	0.05	0.4
8	0.09	0.11	0.13	0.15	0.17	0.19
9	0.05	0.07	0.09	0.11	0.13	0.15
10	0.01	0.03	0.05	0.07	0.09	0.11
11	0.02	0.04	0.08	0.12	0.17	0.25
12	0.02	0.04	0.07	0.1	0.15	0.2
13	0.1	0.15	0.2	0.25	0.3	0.35
14	0.01	0.03	0.05	0.06	0.08	0.1
!	ı					
$p_T = 0.17$ Scenarios #	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6
15	0	0.02	0.05	0.08	0.11	0.14
16	0.22	0.02	0.03	0.08	0.11	0.14
17	0.22	0.32	0.37	0.47	0.37	0.07
18	0.01	0.17	0.37	0.57	0.77	0.92
19	0.01	0.03	0.03	0.87	0.17	0.47
20	0.02	0.47	0.77	0.87	0.92	0.90
20	0	0.02	0.07	0.47	0.07	0.67
22	0.16	0.18	0.04	0.07	0.12	0.87
23	0.10	0.18	0.2	0.22	0.24	0.20
23	0.12	0.14	0.10	0.18	0.16	0.22
24 25	0.08	0.1	0.12	0.14	0.16	0.18
26	0.02	0.08	0.14	0.2	0.20	0.34
	0.02					0.34
27		0.22	0.27	0.32	0.37	
28	0.02	0.05	0.08	0.11	0.14	0.17
$p_T = 0.3$						
Scenarios#	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6
29	0.02	0.05	0.1	0.15	0.2	0.25
30	0.35	0.45	0.5	0.6	0.7	0.8
31	0.01	0.3	0.55	0.65	0.8	0.95
32	0.04	0.06	0.08	0.1	0.3	0.6
33	0.05	0.6	0.8	0.9	0.95	0.99
34	0.01	0.05	0.1	0.6	0.7	0.9

35	0.01	0.03	0.07	0.1	0.15	0.75
36	0.29	0.31	0.33	0.35	0.37	0.39
37	0.25	0.27	0.29	0.31	0.33	0.35
38	0.21	0.23	0.25	0.27	0.29	0.31
39	0.05	0.2	0.27	0.33	0.39	0.45
40	0.05	0.1	0.2	0.3	0.4	0.4
41	0.3	0.35	0.4	0.45	0.5	0.55
42	0.15	0.18	0.21	0.24	0.27	0.3

 ${\bf Appendix} \ B$ ${\bf Details} \ {\bf of} \ {\bf the} \ {\bf CRM} \ {\bf and} \ {\bf BLRM} \ {\bf design} \ {\bf implemented} \ {\bf in} \ {\bf simulation} \ {\bf study}.$

The Continuous Reassessment Method (CRM)

In the CRM design, we used the one-parameter power model

$$p_i = c_i^{\theta} \text{ for } \theta > 0, i = 1, \dots I,$$

where θ is the parameter of the model, p_i is the toxicity rate at dose i, and c_i 's are pre-specified prior toxicity probability ('skeleton') values, monotonically increasing with i. The skeleton c_i 's reflect the initial guesses of toxicity probability at each dose. We adopted the method proposed in Lee and Cheung (2011) for selecting the skeleton based on indifference intervals. We used half-width $\lambda = 0.05$ and we used log-normal prior $\pi(\theta) \sim lognormal(0, 1.34)$.

The posterior distribution of θ is given by

$$p(\theta|n,y) \propto \prod_{i=1}^{I} (c_i^{\theta})^{y_i} (1-c_i^{\theta})^{n_i-y_i} \pi(\theta),$$

where $n = \{n_1, ..., n_I\}$ are the number patients, and $y = \{y_1, ..., y_I\}$ are the number of patients experienced DLTs.

The CRM design starts the trial by treating the first cohort at the lowest dose d_1 . The posterior distribution of $\pi(\theta)$ is updated based on the accumulating information across all dose levels, and the posterior mean of $\pi(\theta)$ is used as the point estimate of θ to guide dose assignment. In

particular, the next cohort will be assigned to the dose with \hat{p}_i closest to p_T . In our simulation, an additional no-skipping escalation rule is added in order to ensure the safety of the trial conduct. In addition, the Safety rules 1 and 2 as stated in Section 2.1 are also applied in CRM design. Lastly, no escalation is permitted if the empirical DLT rate of the most recent cohort is higher than p_T .

The Bayesian Logistic Regression Method (BLRM)

BLRM assumes a two-parameter logistic model

$$logit(p_i) = log(\alpha) + \beta log(\frac{d_i}{d_{ref}})$$

where α , β are unknown parameters, d_i is the raw dosage at dose level i, and d_{ref} is the reference dose level. Model parameters α and β follow a multivariate log-normal prior,

$$\binom{\alpha}{\beta} \sim lognormal \left(\binom{\mu_1}{\mu_2} \ \Sigma \right), \text{ where } \Sigma = \begin{pmatrix} \sigma_1^2 & \rho \sigma_1 \sigma_2 \\ \rho \sigma_1 \sigma_2 & \sigma_2^2 \end{pmatrix}$$

Let $\theta = \{\mu 1, \mu 2, \sigma 1, \sigma 2, \rho\}$ be the hyperparameter set of the model. In the simulation, we used a default set of doses, $d_i = 5 \times i$, and the default reference dose level is the ceiling of $\frac{(l+1)}{2}$, where l is the number of doses. In addition, we used the quantile-based non-informative prior calculator proposed by Neuenschwander et al. (2008) to obtain the values of θ , and use the same prior guess for the lowest and highest doses as described in Appendix A.1 in Neuenschwander et al. (2008). The posterior distribution of (α, β) is given

$$p(\theta|n,y) \propto \prod_{i=1}^{l} (c_i^{\theta})^{y_i} (1 - c_i^{\theta})^{n_i - y_i} \pi(\theta)$$

where $n = \{n_1, ..., n_I\}$ are the number patients, and $y = \{y_1, ..., y_I\}$ are the number of patients experienced DLTs.

The BLRM starts a trial by treating the first cohort at the lowest patient. After each cohort is treated, the standard dose recommendation of BLRM relies on maximizing the probability of targeted toxicity interval $(p_T + \varepsilon_1, p_T + \varepsilon_2)$. In our simulation, we used $\varepsilon_1 = \varepsilon_2 = 0.05$. In particular, the next cohort will be assigned to the dose whose posterior probability in the targeted

toxicity interval is the largest, i.e. $\underset{i=1,...,l}{argmax} \Pr\left(p_i \in (p_T + \varepsilon_1, p_T + \varepsilon_2) | y, n\right)$. The BLRM imposes an overdose control rule (Escalation with Overdose Control, EWOC) such that the probability of excessive toxicity of the recommended dose should be less than a given threshold p_{EWOC} , i.e. $\Pr\left(p_i > p_T + \varepsilon_2 | y, n\right) < p_{EWOC}$. In our simulation, we used $p_{EWOC} = 0.5$. In addition, the Safety rules 1 and 2 as stated in Section 2.1 are also applied in BLRM design. Besides safety rule I, if all doses violate the EWOC rule, the trial will be terminated before the maximum the sample size is reached.

Appendix C Operating characteristics comparing i3+3 with other phase I designs

Six designs (mTPI2, mTPI, BOIN, CRM, BLRM and 3+3) are compared with i3+3. A sample size of 30 patients is used for each trial with a cohort size of 3. For the mTPI and mTPI-2 designs, the EI is $[p_T - 0.05, p_T + 0.05]$. For the BOIN design, we set $(p_T - \lambda_e) = 0.05$ and $(\lambda_d - p_T) = 0.05$ so that the actual intervals for decision making between BOIN and mTPI or mTPI-2 are identical. For the BLRM design, the EWOC parameter is set at 0.5. Under each simulation scenario, we generate 1,000 simulated trials.

Scenario 1 Target Toxicity Prob. = 0.1 Selection Prob. # of Patients Treated # of Toxicities Dose Level True Tox Prob i3+3 mTPI mTPI-2 3+3 BOIN BLRM CRM i3+3 mTPI mTPI-2 3+3 BOIN BLRM CRM i3+3 mTPI mTPI-2 3+3 BOIN BLRM CRM 7.05 0.259 0.04 0.092 0.084 0.107 0.019 0.109 0.077 0.076 6.261 6.261 3 372 6 888 5 766 6.102 0.256 0.249 0.277 0.133 0.275 0.224 0.05 0.123 0.119 0.168 0.035 0.135 0.235 0.168 5.916 5 943 6.081 3.432 5.64 9.123 6.474 0.337 0.32 0.334 0.168 0.274 0.469 0.356 0.06 0.123 0.204 0.157 0.051 0.129 0.362 0.171 5.022 5.4 5.055 3.537 4.791 10.011 5.403 0.288 0.343 0.322 0.223 0.274 0.637 0.33 4 134 3 831 0.289 0.276 0.259 0.07 0.218 0.145 0.162 0.059 0.174 0.217 0.172 3 969 3 444 4 065 2 694 4 248 0.311 0.256 0.197 0.305 0.08 0.135 0.132 0.125 0.065 0.141 0.023 0.122 2.787 2.856 2,979 3.324 3.378 0.18 3.042 0.196 0.225 0.23 0.271 0.286 0.017 0.243 0.09 0.286 0.291 0.256 0.75 0.296 5.376 5.01 4.443 3.003 4.878 0.003 0.465 0.458 0.409 0.279 0.411 0.371 0.266 4.14 0 0 BLRM i3+3 mTPI mTPI-2 3+3 BOIN CRM Prob. of Select MTD 0.885 0.891 0.868 0.96 0.875 0.837 0.899 0.056 0.063 Prob. of Toxicity 0.063 0.064 0.063 0.066 0.06 Prob. of Select Dose-over-MTD 0 0 0 0 0 0 0 Prob. of No Selection 0.023 0.025 0.025 0.021 0.086 0.025 0.016 29.409 Scenario 2 29.439 29.64 # of Toxicities Target Toxicity Prob. = 0.1 Selection Prob # of Patients Treated Dose Level True Tox Prob i3+3 mTPImTPI-2 3+3 BOIN BLRM CRM i3+3 mTPI mTPI-2 3+3 BOIN BLRM CRM i3+3 mTPI mTPI-23+3 BOIN BLRM CRM 0.356 0.345 0.371 0.265 0.437 0.276 0.386 12,417 12,939 4.611 14,403 10.017 13,743 1.912 2.219 0.684 2.089 1.554 2.082 0.15 14,649 1.969 5.526 1 221 0.2 0.138 0.145 0.119 0.233 0 144 0.104 0.162 6 339 6 144 5.058 3 921 5 739 5.793 1 203 1.01 0.812 1.08 1 216 1 148 0.25 0.039 0.074 0.037 0.153 0.041 0.021 0.054 2.784 2.652 2.088 2.73 2 22 1.326 2.403 0.732 0.637 0.507 0.698 0.534 0.322 0.584 0.227 4 0.3 0.014 0.009 0.007 0.103 0.012 0.001 0.01 0.963 0.963 0.807 1.662 0.741 0.084 0.756 0.277 0.289 0.246 0.495 0.027 0.219 5 0.35 0.003 0.003 0.001 0.034 0.005 0 0 0.267 0.231 0.21 0.816 0.243 0 0.171 0.102 0.087 0.081 0.307 0.071 0 0.069 0.017 0.039 0.24 0.057 0.025 0.099 0.025 0.014 0 0.069 0.03 0.027 0.016 0.018 i3+3 mTPI mTPI-2 3+3 BOIN BLRM CRM Prob. of Select MTD 0.356 0.345 0.371 0.265 0.437 0.276 0.386 Prob. of Toxicity 0.186 0.184 0.179 0.221 0.174 0.182 0.18 Prob. of Select Dose-over-MTD 0.194 0.231 0.164 0.54 0.202 0.126 0.226 Prob. of No Selection 0.195 0.45 0.424 0.465 0.361 0.598 0.388 Scenario 3 Target Toxicity Prob. = 0.1 Selection Prob # of Patients Treated # of Toxicities BLRM CRM BLRM CRM BOIN BLRM CRM Dose Level True Tox Prob i3 + 3mTPI mTPI-2 3+3 ROIN i3 + 3mTPI mTPI-2 3+3ROIN i3+3 m TPI mTPI-2 3+30.01 0.265 0.195 0.273 0.093 0.2 0.194 0.166 7.38 6.246 8.295 3.336 8.247 8.085 7.047 0.087 0.066 0.085 0.024 0.089 0.084 0.075 0.1 0.446 0.497 0.526 0.284 0.523 0.608 0.538 11.109 12.348 12.1864.524 12.17 14.781 12.618 1.134 1.225 1.225 0.453 1.157 1.438 1.266 7.152 0.184 0.213 0.137 0.242 0.157 0.224 6.894 5.904 4.365 6.027 5.874 1.447 1.197 0.89 1.173 1.353 0.2 0.196 6.678 1.33 1.173 0.25 0.197 3.054 2.745 2.301 3.069 2.394 0.429 2.514 0.727 0.694 0.741 0.59 0.636 0.076 0.07 0.044 0.061 0.01 0.056 0.6 0.101 0.852 0.255 5 0.3 0.021 0.02 0.014 0.109 0.019 0.009 1.11 1.107 0.942 2.01 0.012 0.804 0.322 0.314 0.615 0.241 0.002 0.226 0 0.35 0.002 0.002 0.002 0.074 0 0 0.004 0.396 0.327 0.297 0.813 0.279 0 0.264 0.13 0.124 0.112 0.294 0.094 0 0.098 i3+3 3+3 BOIN BLRM CRM mTPI mTPI-2 Prob. of Select MTD 0.446 0.497 0.526 0.284 0.523 0.608 0.538 Prob. of Toxicity 0.125 0.129 0.116 0.167 0.112 0.096 0.122 Prob. of Select Dose-over-MTD 0.283 0.305 0.197 0.622 0.276 0.167 0.293 Prob. of No Selection 0.006 0.003 0.004 0.001 0.001 0.031 0.003 Scenario 4 Target Toxicity Prob. = 0.1 Selection Prob. # of Patients Treated of Toxicities mTPI mTPI-2 BLRM CRM mTPI-2 CRM mTPI-2 BLRM CRM True Tox Prob i3+3 3+3 BOIN BOIN BLRM mTPI BOIN Dose Level i3+3 mTPI 3+3 i3+33+3 0.006 0.015 0.016 0.004 0.023 0.004 0.009 3.648 3.858 4.089 3.099 4.272 3.786 3.714 0.036 0.042 0.045 0.034 0.052 0.034 0.039 0.01 0.02 0.036 0.022 0.076 0.011 0.066 0.101 0.044 4.335 4.404 4.647 3.207 4.581 7.719 4.425 0.089 0.091 0.093 0.067 0.102 0.143 0.095 0.03 0.068 0.144 0.115 0.014 0.093 0.346 0.109 4.554 4.764 4.785 3.282 4.581 12.066 5.007 0.134 0.125 0.13 0.1 0.123 0.359 0.135 4 0.04 0.343 0.245 0.299 0.091 0.243 0.472 0.309 5.307 5.34 5.811 3.528 5.646 5.316 6.732 0.217 0.218 0.229 0.142 0.223 0.214 0.271 0.1 0.466 0.48 0.422 0.367 0.457 0.049 0.423 7,269 6.966 6.858 4.518 6.948 0.42 6.729 0.717 0.701 0.439 0.642 0.046 0.674 0.7 6 0.25 0.079 0.091 0.069 0.51 0.117 0.003 0.103 4 848 4.593 3,735 3.804 3 948 0.024 3.318 1 22 1.167 0.977 0.975 1 009 0.002 0.882 i3+3 mTPI mTPI-2 3+3 BOIN BLRM CRM Prob. of Select MTD 0.466 0.422 0.367 0.049 0.423 0.48 0.457 Prob. of Toxicity 0.08 0.079 0.073 0.082 0.0718 0.027 0.07 Prob. of Select Dose-over-MTD 0.079 0.091 0.069 0.51 0.117 0.003 0.103 Prob. of No Selection 0.002 0.003 0.003 0.003 0.025 0.001 0.003 Scenario 5 Target Toxicity Prob. = 0.1 Selection Prob # of Patients Treated # of Toxicities Dose Level True Tox Prob i3+3 mTPI mTPI-2 3+3 BOIN BLRM CRM i3+3 mTPI mTPI-2 3+3 BOIN BLRM CRM i3+3 mTPI mTPI-2 3+3 BOIN BLRM CRM 0.05 0.937 0.939 0.937 0.742 0.956 0.681 0.918 22,308 22.38 22.926 5.394 23.004 17.952 23.037 1.11 1.14 1.152 0.277 1.13 0.931 1.172 0.025 5,724 6.033 5.439 4.737 2.408 2.229 0.4 0.01 0.007 0.009 0.197 0.015 0.039 5.67 4.986 5.46 2.29 2.194 1.924 2.035 2.188 0.5 0.001 0.001 0.001 0.028 0.003 0 0.975 0.648 0.612 1.314 0.738 0.411 0.567 0.504 0.352 0.332 0.654 0.357 0.185 0.31 0 0.6 0 0 0 0.002 0 0 Λ 0.099 0.057 0.051 0.225 0.084 0 0.054 0.056 0.038 0.036 0.139 0.057 0 0.037 0.65 0 0 0 0.001 0 0.006 0.021 0.003 0.003 0.011 0.002 0 0 0 0 0 0 0 0 0 0 0.7 0 0 0 0 0.003 0 0 0.002 0 0 0 0 0 0 0 0 0 0

i3+3

0.937

0.136

0.011

0.052

Prob. of Select MTD

Prob. of No Selection

Prob. of Select Dose-over-MTD

Prob. of Toxicity

mTPI

0.939

0.135

0.008

0.053

mTPI-2

0.937

0.128

0.01

0.053

3+3

0.742

0.257

0.228

0.03

BOIN

0.956

0.128

0.018

0.026

BLRM

0.681

0.135

0.025

0.294

CRM

0.918

0.127

0.039

0.043

Scenario 6

Scenario 6																					
Target Toxicity Prob. = 0.1				election Prob							Patients Tre							# of Toxicities			
Dose Level True Tox Prob.	i3+3	mTPI	mTPI-2	3+3	BOIN	BLRM	CRM	i3+3	mTPI	mTPI-2	3+3	BOIN	BLRM	CRM	i3+3	mTPI	mTPI-2	3+3	BOIN	BLRM	CRM
1 0.01	0.014	0.017	0.031	0.013	0.036	0.013	0.015	3.762	3.984	4.452	3.132	4.647	4.11	3.912	0.032	0.044	0.05	0.033	0.055	0.038	0.044
2 0.03	0.122	0.089	0.177	0.024	0.132	0.186	0.148	5.472	5.457	6.279	3.342	6.093	9.135	6.915	0.164	0.161	0.19	0.11	0.19	0.251	0.209
3 0.05	0.828	0.868	0.768	0.739	0.792	0.718	0.809	14.832	14.943	14.076	5.31	14.103	14.103	14.076	0.759	0.741	0.695	0.257	0.696	0.702	0.708
4 0.4	0.036	0.023	0.021	0.194	0.038	0.058	0.025	4.998	4.791	4.416	4.725	4.464	1.956	4.407	1.964	1.919	1.758	1.884	1.758	0.78	1.77
5 0.5	0	0	0	0.023	0.001	0	0	0.855	0.669	0.621	1.29	0.594	0.027	0.537	0.431	0.332	0.31	0.673	0.279	0.011	0.261
6 0.6		0	0	0.005	-	-	0	0.081	0.081	0.081	0.183	0.075	0	0.078	0.051	0.05	0.05	0.111	0.039	0	0.048
p. 1. (2.1)	i3+3	mTPI	mTPI-2	3+3	BOIN	BLRM	CRM														
Prob. of Select MTD Prob. of Toxicity	0.828	0.868 0.109	0.768 0.102	0.739 0.171	0.792	0.718 0.061	0.809 0.102														
Prob. of Select Dose-over-MTD	0.113 0.036	0.109	0.102	0.171	0.1 0.039	0.061	0.102														
Prob. of No Selection	0.030	0.023	0.021	0.002	0.001	0.038	0.023														
Scenario 7		0.005	0.003	0.002	0.001	0.023	0.005	l							l						ı
Target Toxicity Prob. = 0.1	1		S	election Prob				ı		# of	Patients Tre	eated			İ			# of Toxicities			
Dose Level True Tox Prob.	i3+3	mTPI	mTPI-2	3+3	BOIN	BLRM	CRM	i3+3	mTPI	mTPI-2	3+3	BOIN	BLRM	CRM	i3+3	mTPI	mTPI-2	3+3	BOIN	BLRM	CRM
1 0.01	0.011	0.015	0.016	0.004	0.023	0.004	0.009	3.603	3.858	4.086	3.102	4.272	3.786	3.714	0.026	0.042	0.045	0.033	0.052	0.034	0.039
2 0.02	0.025	0.022	0.075	0.008	0.066	0.101	0.044	4.434	4.404	4.638	3.225	4.581	7.719	4.425	0.104	0.091	0.092	0.075	0.102	0.143	0.095
3 0.03	0.063	0.142	0.108	0.025	0.091	0.346	0.108	4.692	4.764	4.731	3.315	4.512	12.054	4.935	0.14	0.125	0.128	0.096	0.123	0.359	0.13
4 0.04	0.252	0.144	0.177	0.029	0.145	0.464	0.26	4.68	4.434	4.716	3.435	4.473	5.304	6.477	0.183	0.184	0.2	0.166	0.167	0.213	0.276
5 0.05	0.639	0.663	0.604	0.642	0.646	0.057	0.53	8.805	8.787	8.418	4.971	8.55	0.441	7.368	0.439	0.464	0.429	0.243	0.42	0.025	0.364
6 0.4	0.01	0.011	0.017	0.29	0.028	0.003	0.046	3.786	3.678	3.336	4.038	3.588	0.027	3.006	1.525	1.488	1.369	1.615	1.405	0.006	1.253
n 1 (0 1) (mn	i3+3	mTPI	mTPI-2	3+3	BOIN	BLRM	CRM	1													
Prob. of Select MTD	0.639	0.663	0.604	0.642	0.646	0.057	0.53	I													
Prob. of Toxicity	0.081	0.08	0.076	0.101	0.076	0.027	0.072	1													
Prob. of Select Dose-over-MTD Prob. of No Selection	0.01	0.011 0.003	0.017 0.003	0.29 0.002	0.028 0.001	0.003 0.025	0.046 0.003	1													
Scenario 8		0.003	0.003	0.002	0.001	0.023	0.003	l						l	l						II.
Target Toxicity Prob. = 0.1	1		S	Selection Prob				ı		# of	Patients Tre	eated						# of Toxicities			
Dose Level True Tox Prob.	i3+3	mTPI	mTPI-2	3+3	BOIN	BLRM	CRM	i3+3	mTPI	mTPI-2	3+3	BOIN	BLRM	CRM	i3+3	mTPI	mTPI-2	3+3	BOIN	BLRM	CRM
1 0.09	0.277	0.273	0.323	0.1	0.303	0.182	0.26	10.461	10.29	11.736	3.981	11.331	7.842	10.344	0.948	0.95	1.075	0.39	1.04	0.704	0.957
2 0.11	0.188	0.188	0.195	0.13	0.198	0.317	0.247	6.435	7.056	6.468	3.774	6.405	9.36	7.335	0.713	0.801	0.747	0.406	0.668	1.002	0.839
3 0.13	0.149	0.179	0.144	0.121	0.149	0.181	0.163	4.659	4.656	4.317	3.447	4.293	5.202	4.668	0.594	0.596	0.543	0.474	0.526	0.673	0.589
4 0.15	0.143	0.103	0.096	0.137	0.106	0.033	0.107	2.994	2.76	2.496	3	2.652	0.765	2.805	0.436	0.41	0.372	0.442	0.395	0.12	0.411
5 0.17	0.069	0.074	0.057	0.111	0.061	0.004	0.067	1.542	1.533	1.47	2.523	1.554	0.042	1.485	0.275	0.256	0.237	0.446	0.237	0.003	0.24
6 0.19	0.029	0.046	0.031	0.306	0.05	0	0.041	1.338	1.329	1.071	1.752	1.095	0	0.981	0.251	0.244	0.202	0.338	0.184	0	0.188
	i3+3	mTPI	mTPI-2	3+3	BOIN	BLRM	CRM														
Prob. of Select MTD	0.757	0.743	0.758	0.488	0.756	0.713	0.777														
Prob. of Toxicity	0.117	0.118	0.115	0.135	0.112	0.108	0.117														
Prob. of Select Dose-over-MTD	0.098 0.145	0.12 0.137	0.088 0.154	0.417 0.095	0.366 0.133	0.004 0.283	0.108														
Prob. of No Selection Scenario 9	0.143	0.137	0.134	0.093	0.133	0.283	0.115	ļ						Į.							
Target Toxicity Prob. = 0.1			\$	Selection Prob				I		# of	Patients Tre	eated		I				# of Toxicities			Ĭ
Dose Level True Tox Prob.	i3+3	mTPI	mTPI-2	3+3	BOIN	BLRM	CRM	i3+3	mTPI	mTPI-2	3+3	BOIN	BLRM	CRM	i3+3	mTPI	mTPI-2	3+3	BOIN	BLRM	CRM
1 0.05	0.16	0.149	0.186	0.047	0.174	0.097	0.128	7.446	7.584	8.721	3.537	8.61	6.285	7.326	0.364	0.379	0.432	0.18	0.415	0.328	0.366
2 0.07	0.171	0.173	0.229	0.071	0.221	0.317	0.229	6.516	6.945	6.969	3.63	6.942	10.161	7.5	0.495	0.519	0.513	0.244	0.489	0.678	0.551
3 0.09	0.164	0.26	0.202	0.11	0.177	0.329	0.239	5.511	5.619	5.208	3.75	5.34	8.346	5.757	0.478	0.483	0.468	0.346	0.467	0.769	0.497
4 0.11	0.225	0.146	0.158	0.111	0.181	0.11	0.149	4.116	4.059	3.789	3.543	3.834	1.647	4.215	0.432	0.493	0.448	0.42	0.441	0.167	0.513
5 0.13	0.149	0.119	0.096	0.122	0.104	0.01	0.114	2.943	2.418	2.391	3.18	2.427	0.111	2.427	0.379	0.328	0.329	0.409	0.315	0.023	0.323
6 0.15	0.094	0.12	0.094	0.513	0.119	0	0.109	2.76	2.634	2.181	2.514	2.346	0	2.034	0.437	0.381	0.313	0.382	0.334	0	0.295
n 1 (01) (mn	i3+3	mTPI	mTPI-2	3+3	BOIN	BLRM	CRM]													1
Prob. of Select MTD	0.963	0.967	0.965	0.974	0.976	0.863	0.968														
Prob. of Toxicity	0.088	0.088	0.086	0.098	0.083	0.074	0.087	1													
Prob. of Select Dose-over-MTD Prob. of No Selection	0 0.037	0.033	0 0.035	0 0.026	0 0.024	0 0.137	0 0.032	1													
Scenario 10	0.037	0.055	0.033	0.020	0.024	0.13/	0.032	l						l	l						II.
Target Toxicity Prob. = 0.1			S	Selection Prob						# of	Patients Tre	eated						# of Toxicities			
Dose Level True Tox Prob.	i3+3	mTPI	mTPI-2	3+3	BOIN	BLRM	CRM	i3+3	mTPI	mTPI-2	3+3	BOIN	BLRM	CRM	i3+3	mTPI	mTPI-2	3+3	BOIN	BLRM	CRM
1 0.01	0.021	0.017	0.025	0.014	0.035	0.013	0.011	4.041	3.984	4.404	3.129	4.629	4.11	3.879	0.049	0.044	0.05	0.031	0.055	0.038	0.044
2 0.03	0.082	0.069	0.145	0.018	0.112	0.179	0.086	5.169	5.394	5.781	3.306	5.643	9	5.421	0.164	0.158	0.168	0.105	0.18	0.247	0.158
3 0.05	0.143	0.223	0.182	0.049	0.162	0.421	0.193	5.724	5.853	5.772	3.489	5.643	11.862	6.072	0.283	0.288	0.281	0.168	0.272	0.595	0.301
4 0.07	0.292	0.176	0.197	0.076	0.178	0.326	0.221	5.301	5.01	4.902	3.609	4.695	4.092	5.592	0.397	0.361	0.354	0.251	0.321	0.259	0.396
5 0.09	0.212	0.219	0.215	0.094	0.203	0.035	0.224	4.134	4.035	4.224	3.615	4.194	0.252	4.392	0.385	0.351	0.372	0.327	0.338	0.021	0.386
6 0.11	0.248	0.293	0.233	0.748	0.309	0.001	0.262	5.58	5.649	4.842	3.207	5.172	0.015	4.569	0.669	0.672	0.587	0.36	0.54	0.001	0.554
Prob. of Select MTD	i3+3 0.895	mTPI	mTPI-2 0.827	3+3 0.967	BOIN 0.852	BLRM 0.783	CRM 0.9														
	0.893	0.911	0.847					l													
	0.065	0.063	0.061	0.061	0.057	0.04	0.061														II.
Prob. of Toxicity	0.065	0.063	0.061	0.061	0.057	0.04	0.061														
	II .						0.061 0 0.003														

Scenario II

	enano i i																					
	xicity Prob. = 0.1				Selection Prol							Patients Tro							# of Toxicities			
Dose Level	True Tox Prob.	i3+3	mTPI	mTPI-2	3+3	BOIN	BLRM	CRM	i3+3	mTPI	mTPI-2	3+3	BOIN	BLRM	CRM	i3+3	mTPI	mTPI-2	3+3	BOIN	BLRM	CRM
1 2	0.02 0.04	0.052 0.169	0.03 0.146	0.043 0.238	0.012 0.071	0.063 0.193	0.041 0.282	0.023 0.179	4.728 6.357	4.566 6.573	5.178 7.158	3.183 3.525	5.613 6.912	4.854 10.56	4.431 6.882	0.101 0.286	0.087 0.273	0.099 0.275	0.058 0.15	0.119 0.272	0.103 0.417	0.086 0.284
2	0.04	0.169	0.140	0.238	0.071	0.193	0.282	0.179	7.152	7.578	7.138	3.915	6.822	10.908	7.932	0.286	0.273	0.273	0.13	0.272	0.417	0.629
3 4	0.08	0.263	0.374	0.334	0.134	0.239	0.437	0.331	5.817	5.547	5.214	3.913	5.304	2.061	6.051	0.336	0.379	0.568	0.502	0.543	0.864	0.629
5	0.17	0.151	0.174	0.126	0.232	0.162	0.01	0.146	3.429	3.498	3.156	3.669	3.462	0.12	3.024	0.595	0.593	0.529	0.639	0.584	0.019	0.509
6	0.25	0.043	0.045	0.033	0.351	0.048	0	0.041	2.313	2.052	1.686	2.472	1.773	0	1.494	0.544	0.481	0.404	0.623	0.429	0.015	0.36
, ,	0.23	i3+3	mTPI	mTPI-2	3+3	BOIN	BLRM	CRM	2.313	2.002	1.000	2.172	1.,,,5		,	0.5	0.101	0.101	0.023	0.127	· ·	0.50
Prob. of Select M	MTD	0.577	0.597	0.552	0.327	0.529	0.611	0.603														
Prob. of Toxicity	y	0.094	0.091	0.085	0.111	0.085	0.058	0.088														
Prob. of Select D	Oose-over-MTD	0.194	0.219	0.159	0.583	0.21	0.01	0.187														
Prob. of No Sele	ection	0.008	0.008	0.008	0.007	0.005	0.056	0.008														
	enario 12								•													
	xicity Prob. = 0.1				Selection Prol							Patients Tro							# of Toxicities			
Dose Level	True Tox Prob.	i3+3	mTPI	mTPI-2	3+3	BOIN	BLRM	CRM	i3+3	mTPI	mTPI-2	3+3	BOIN	BLRM	CRM	i3+3	mTPI	mTPI-2	3+3	BOIN	BLRM	CRM
1	0.02	0.042	0.029	0.041	0.017	0.063	0.04	0.021	4.632	4.554	5.154	3.216	5.607	4.827	4.407	0.085	0.087	0.099	0.063	0.119	0.1	0.085
2	0.04	0.136	0.12	0.206	0.05	0.164	0.242	0.155	5.91	6.234	6.696	3.456	6.393	10.137	6.474	0.264	0.257	0.261	0.146	0.258	0.404	0.268
3	0.07 0.1	0.234 0.341	0.332 0.234	0.295 0.238	0.086 0.158	0.214 0.282	0.443 0.2	0.287 0.288	6.582 5.958	7.071 5.532	6.978 5.334	3.726 3.864	6.288 5.367	10.914 2.451	7.425 6.135	0.435 0.635	0.46 0.603	0.454 0.593	0.268 0.397	0.426 0.477	0.738 0.236	0.5 0.664
5	0.15	0.341	0.234	0.238	0.138	0.282	0.2	0.288	3.938	3.735	3.408	3.804	3.783	0.171	3,333	0.605	0.603	0.593	0.555	0.477	0.236	0.664
6	0.13	0.103	0.180	0.068	0.476	0.174	0.019	0.136	2.865	2.688	2.244	2.859	2.448	0.171	2.04	0.567	0.527	0.32	0.601	0.363	0.023	0.318
· ·	0.2	i3+3	mTPI	mTPI-2	3+3	BOIN	BLRM	CRM	2.803	2.000	2.244	2.039	2.440	0.003	2.04	0.507	0.527	0.440	0.001	0.439	Ü	0.577
Prob. of Select M	MTD	0.74	0.752	0.677	0.45	0.67	0.662	0.731														
Prob. of Toxicity		0.087	0.084	0.08	0.097	0.077	0.053	0.082														
Prob. of Select D		0.076	0.091	0.068	0.476	0.098	0	0.085														
Prob. of No Sele	ection	0.006	0.008	0.008	0.007	0.005	0.056	0.008														
Sce	enario 13								•							II.						"
Target Tox	xicity Prob. = 0.1			5	Selection Prol	b.					# of	Patients Tro	eated						# of Toxicitie:	s		ĺ
Dose Level	True Tox Prob.	i3+3	mTPI	mTPI-2	3+3	BOIN	BLRM	CRM	i3+3	mTPI	mTPI-2	3+3	BOIN	BLRM	CRM	i3+3	mTPI	mTPI-2	3+3	BOIN	BLRM	CRM
1	0.1	0.385	0.378	0.442	0.176	0.42	0.297	0.376	11.769	11.838	14.001	4.173	13.614	9.834	12.312	1.21	1.215	1.409	0.422	1.4	0.979	1.269
2	0.15	0.262	0.247	0.213	0.227	0.241	0.282	0.3	8.172	8.361	7.26	4.152	7.326	8.856	8.424	1.224	1.233	1.109	0.63	1.042	1.335	1.234
3	0.2	0.092	0.141	0.093	0.187	0.102	0.074	0.125	4.254	4.095	3.438	3.522	3.483	3.243	3.912	0.885	0.812	0.665	0.736	0.673	0.606	0.81
4 5	0.25 0.3	0.032 0.013	0.038 0.012	0.03	0.179 0.073	0.049 0.008	0.01	0.025	1.617 0.684	1.839 0.591	1.476 0.519	2.55 1.563	1.494 0.537	0.291 0.015	1.566 0.462	0.434	0.458 0.172	0.359 0.154	0.594 0.528	0.36 0.154	0.065 0.005	0.389 0.134
6	0.35	0.013	0.012	0.001	0.073	0.008	0	0.009	0.084	0.183	0.319	0.579	0.337	0.013	0.462	0.18	0.172	0.134	0.328	0.134	0.003	0.134
O	0.55	i3+3	mTPI	mTPI-2	3+3	BOIN	BLRM	CRM	0.231	0.163	0.133	0.579	0.139	U	0.141	0.08	0.001	0.040	0.199	0.032	U	0.042
Prob. of Select M	MTD	0.647	0.625	0.655	0.403	0.661	0.579	0.676														
Prob. of Toxicity		0.15	0.147	0.139	0.188	0.138	0.134	0.145														
Prob. of Select D		0.14	0.192	0.134	0.494	0.159	0.084	0.162														
Prob. of No Sele		0.213	0.183	0.211	0.103	0.18	0.337	0.162														
Sce	enario 14								ı							ı						,
Target Tox	xicity Prob. = 0.1			5	Selection Prol	b.					# of	Patients Tro	eated						# of Toxicities	S		
Dose Level	True Tox Prob.	i3+3	mTPI	mTPI-2	3+3	BOIN	BLRM	CRM	i3+3	mTPI	mTPI-2	3+3	BOIN	BLRM	CRM	i3+3	mTPI	mTPI-2	3+3	BOIN	BLRM	CRM
1	0.01	0.014	0.017	0.025	0.014	0.035	0.013	0.011	3.789	3.984	4.404	3.132	4.629	4.11	3.879	0.033	0.044	0.05	0.033	0.055	0.038	0.044
2	0.03	0.071	0.068	0.143	0.023	0.112	0.179	0.085	5.136	5.379	5.742	3.312	5.634	8.997	5.394	0.151	0.157	0.167	0.101	0.18	0.247	0.157
3	0.05	0.101	0.202	0.154	0.033	0.15	0.403	0.167	5.4	5.616	5.472	3.447	5.391	11.769	5.793	0.257	0.273	0.266	0.175	0.261	0.588	0.284
4	0.06	0.299	0.172	0.19	0.058	0.161	0.341	0.216	5.226	4.818	4.782	3.486	4.47	4.161	5.412	0.297	0.293	0.285	0.204	0.266	0.221	0.324
5	0.08 0.1	0.22 0.295	0.201 0.337	0.208 0.277	0.078 0.792	0.19 0.351	0.037 0.002	0.212 0.306	4.26 6.189	4.05 6.078	4.257 5.268	3.567 3.252	4.137 5.715	0.276 0.018	4.467 4.98	0.327 0.661	0.328 0.638	0.34 0.566	0.288 0.327	0.301 0.54	0.023 0.001	0.355 0.534
0	0.1	i3+3	mTPI	mTPI-2	3+3	BOIN	BLRM	CRM	0.189	0.078	3.208	3.232	3./13	0.018	4.98	0.001	0.038	0.300	0.327	0.34	0.001	0.334
Prob. of Select M	MTD	0.915	0.912	0.829	0.961	0.852	0.783	0.901														
Prob. of Toxicity		0.913	0.912	0.056	0.961	0.053	0.783	0.901														
Prob. of Select D		0.030	0.030	0.030	0.050	0.055	0.030	0.057														
Prob. of No Sele		ő	0.003	0.003	0.002	0.001	0.025	0.003														
		11							•							li .						

Scenario 1 Target Toxicity Prob. = 0.17 Selection Prob # of Patients Treated # of Toxicities BLRM CRM BLRM CRM Dose Level True Tox Prob. i3+3 mTPI mTPI-2 3+3 BOIN CRM i3+3 mTPImTPI-2 3+3 BOIN BLRM i3+3 mTPI mTPI-2 3+3 BOIN 0.01 0.003 0.001 0.001 0.012 0.002 0.001 0.001 3.081 3.33 3 507 3.105 3.267 3.3 3 249 0.034 0.035 0.027 0.036 0.034 0.02 0.015 0.015 0.028 0.015 0.015 0.017 0.015 3,606 3.759 4.428 3.216 4.149 4.656 3.606 0.064 0.069 0.086 0.075 0.08 0.096 0.068 4.638 5.085 5.829 3.492 5.337 9.126 0.227 0.299 0.254 0.066 0.058 0.121 0.068 0.064 0.17 0.059 4.701 0.279 0.147 0.261 0.45 0.08 0.212 0.239 0.109 0.184 0.361 0.181 5.643 5.604 5.736 3.822 5.913 0.47 0.418 0.441 0.327 0.469 0.636 0.463 0.16 7.776 6.195 0.11 0.262 0.194 0.237 0.136 0.251 0.25 0.268 5.145 4.713 4.881 3.732 4.887 3.276 5.373 0.584 0.491 0.527 0.414 0.533 0.351 0.563 0.374 1.006 0.494 0.52 0.658 0.484 0.192 0.476 7.509 5.619 3.168 6.447 1.623 1.098 1.105 0.837 0.464 0.822 0.209 6.876 3+3 i3+3 mTPI mTPI-2 BOIN BLRM CRM Prob. of Select MTD 0.494 0.374 0.658 0.484 0.192 0.476 0.52 Prob of Toxicity 0.081 0.08 0.074 0.071 0.072 0.06 0.08 Prob. of Select Dose-over-MTD Prob. of No Selection 0 0.002 0 0.009 0 Scenario 2 Target Toxicity Prob. = 0.17 Selection Prob # of Patients Treated # of Toxicities mTPI mTPI-2 BOIN BLRM CRM mTPI-2 BOIN BLRM CRM mTPI mTPI-2 BOIN BLRM CRM Dose Level True Tox Prob. i3+3 i3+3 mTP1 3+3 i3+3 3+3 3+3 0.22 0.386 0.44 0.393 0.37 0.506 0.305 0.5 16 035 15,411 5.06 17 469 11.472 16 134 3.614 3 404 3 944 1 125 3 799 2 535 3 568 0.32 0.076 0.074 0.056 0.149 0.114 0.081 0.098 5.037 5.919 4.017 4.545 4.971 5.004 1.635 1.894 1.268 1.08 1.441 1.598 1.617 0.37 0.018 0.019 0.012 0.078 0.011 0.009 0.021 1.389 1.524 0.951 1.461 1.182 1.131 1.551 0.528 0.55 0.336 0.529 0.427 0.397 0.546 0.47 0.001 0 0 0.011 0.001 0.001 0 0.288 0.264 0.171 0.51 0.231 0.129 0.234 0.125 0.14 0.097 0.258 0.109 0.043 0.128 0.57 0.001 0 0.033 0.036 0.027 0.06 0.042 0.003 0.033 0.021 0.018 0.013 0.035 0.019 0.002 0.016 0 0 0 0.67 0.001 0 0.003 0.003 0.009 0 0 0.003 0 0.002 0.002 0.004 0 0 0.002 i3+3 mTPI mTPI-2 3+3 BOIN BLRM CRM Prob. of Select MTD 0.386 0.44 0.393 0.37 0.506 0.305 0.5 Prob. of Toxicity 0.26 0.259 0.247 0.293 0.247 0.258 0.256 Prob. of Select Dose-over-MTD 0.095 0.093 0.068 0.24 0.126 0.091 0.119 Prob. of No Selection 0.519 0.467 0.539 0.39 0.368 0.604 0.381 Scenario 3 Target Toxicity Prob. = 0.17 Selection Prol # of Patients Treated # of Toxicities Dose Level True Tox Prob. i3+3 mTPI mTPI-2 3+3 BOIN BLRM CRM i3+3 mTPI mTPI-2 3+3 BOIN BLRM CRM i3+3 mTPI mTPI-2 3+3 BOIN BLRM CRM 0.356 0.362 0.245 0.213 9.249 7.848 0.101 0.083 0.079 0.01 0.293 0.255 0.166 7.65 6.363 9.372 3.828 8.1 0 0.065 0.039 0 0.592 15.402 0.17 0.648 0.608 0.545 0.725 0.669 0.692 16.503 15.768 5.334 15.138 16.107 15.372 2.621 2.763 2.639 0.88 2.526 2.709 2.595 0.052 0.059 0.03 0.186 0.109 0.076 0.095 5.979 6.414 4.341 3.9 4.974 5.148 6.036 2.233 2.398 1.631 1.507 1.799 1.871 2 257 0.37 0.57 0 0.013 0 0 0 0.9 0.669 0.477 1.11 0.615 0.387 0.705 0.489 0.385 0.277 0.653 0.376 0.233 0.404 0.77 0 0 0.069 0.051 0.042 0.111 0.024 0.009 0.039 0.052 0.043 0.036 0.086 0.02 0.009 0.033 0.92 0 0 0 0 0 0 0.003 0 0 0 0 0 0 0.003 0 0 0 i3+3 mTPI mTPI-2 3+3 BOIN BLRM CRM Prob. of Select MTD 0.592 0.648 0.608 0.545 0.725 0.669 0.692 Prob. of Toxicity 0.156 0.222 0.179 0.18 0.188 0.157 0.165 Prob. of Select Dose-over-MTD 0.052 0.059 0.03 0.199 0.109 0.076 0.095 Prob. of No Selection 0.001 0.01 Scenario 4 Target Toxicity Prob. = 0.17 Selection Prol # of Patients Treated # of Toxicities mTPI mTPI Dose Level True Tox Prob. i3+3 mTPI-2 3+3 BOIN BLRM CRM mTPI mTPI-2 3+3 ROIN BLRM CRM mTPI-2 3+3 BOIN BLRM CRM 0.001 0.001 0.001 0.008 0.002 0.003 0.001 3.246 3.33 3.594 3.102 3.552 3.363 3.273 0.03 0.034 0.036 0.029 0.025 0.036 0.034 0.035 0.022 0.024 0.016 4.026 4.05 4.686 3.387 4.428 5.016 3.75 0.128 0.103 0.122 0.13 0.152 0.098 0.03 0.018 0.02 0.031 0.117 0.054 4.278 4.977 5.502 3.519 5.1 8.835 4.716 0.279 0.25 0.25 0.05 0.049 0.054 0.112 0.069 0.161 0.064 0.193 0.269 0.188 0.429 0.32 6.177 5.751 6.873 4.038 7.05 7.365 0.394 0.494 0.487 0.07 0.364 0.363 0.395 0.246 0.307 0.46 8.121 0.365 0.476 0.292 0.575 0.308 1.239 0.17 0.546 0.5320.429 0.525 0.5610.552 8.547 7.104 4.863 7.329 3.588 8.214 1.53 1.42 1.208 0.8240.602 1.385 0.022 0.03 0.028 0.133 0.039 0.035 0.047 3.261 3.345 2.241 2.928 2.541 0.834 2.682 1.515 1.603 1.058 1.375 1.159 0.396 1.278 i3+3 mTPI mTPI-2 3+3 BOIN BLRM CRM Prob. of Select MTD 0.546 0.532 0.429 0.525 0.561 0.308 0.552 Prob. of Toxicity 0.129 0.126 0.126 0.106 0.11 0.074 0.118 Prob. of Select Dose-over-MTD 0.022 0.03 0.028 0.133 0.039 0.035 0.047 Prob. of No Selection 0.003 0.009 Scenario 5 Target Toxicity Prob. = 0.17 Selection Pro # of Patients Treated # of Toxicities Dose Level True Tox Prob. i3+3 mTPI mTPI-2 3+3 BOIN BLRM CRM i3+3 mTPI mTPI-2 3+3 BOIN BLRM CRM i3+3 mTPI mTPI-2 3+3 BOIN BLRM CRM 0.995 0.991 0.991 0.862 0.934 0.88 0.92 22 272 22.07 22.5 5 622 22 746 21.528 22,671 0.415 0.437 0.438 0 114 0.45 0.444 0.436 0.47 0.004 0.007 0.007 0.132 0.064 0.057 0.078 7.131 7.392 7.017 3.368 3.466 3.285 3.199 3.024 0.77 0 0 0.002 0 0 0.585 0.471 0.423 0.705 0.468 0.444 0.594 0.449 0.365 0.326 0.539 0.358 0.339 0.461 0 0.87 0.012 0.006 0.006 0.018 0.006 0.006 0.012 0.005 0.005 0.015 0.004 0.005 0 0.92 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0.96 0 0 0 0 0 0 0 0 i3+3 mTPI mTPI-2 3+3 BOIN BLRM CRM Prob. of Select MTD 0.995 0.991 0.991 0.862 0.934 0.88 0.92 Prob. of Toxicity 0.141 0.143 0.135 0.261 0.134 0.134 0.135 Prob. of Select Dose-over-MTD 0.004 0.007 0.007 0.134 0.064 0.057 0.078 Prob. of No Selection 0.001 0.002 0.002 0.004 0.002 0.063 0.002

Scenario 6 Target Toxicity Prob. = 0.17 Selection Prob # of Patients Treated # of Toxicities mTPIBLRM CRM BLRM CRM BLRM CRM Dose Level True Tox Prob. i3+3 mTPI mTPI-2 3+3 BOIN i3 + 3mTPI mTPI-2 3+3 i3+3 mTPI-2 3+3 0.001 0.001 0.009 0.002 0.001 0.001 3.003 3 33 3.12 3.252 0.034 0.035 0.033 0.036 0.034 3.51 3.3 0.02 0.035 0.043 0.077 0.057 0.032 0.05 0.045 3.735 3.999 5.139 3.357 4.881 5.388 4.62 0.053 0.074 0.106 0.08 0.095 0.115 0.095 0.945 0.932 0.877 16,353 15,771 15.831 5.571 15.75 16.797 15.78 1.108 0.391 1.077 1.106 0.07 0.895 0.806 0.898 0.861 1.114 1.097 1.161 4 0.47 0.02 0.024 0.025 0.122 0.066 0.078 0.077 6 2 7 3 6.366 5.1 4.317 5 592 4.131 5.871 2 9 1 5 2 937 2.413 2.062 2 586 1 964 2 696 0.67 0 0 0.002 0.004 0.002 0.001 0 0.612 0.519 0.405 0.732 0.48 0.141 0.468 0.404 0.362 0.279 0.483 0.319 0.097 0.326 0.87 0 0 0 0 0 0.024 0.015 0.015 0.018 0.027 0 0.009 0.021 0.013 0.013 0.015 0.022 0 0.008 i3+3 mTPI mTPI-2 3+3 BOIN BLRM CRM Prob. of Select MTD 0.895 0.877 0.945 0.932 0.806 0.898 0.861 Prob. of Toxicity 0.15 0.151 0.131 0.179 0.137 0.113 0.142 Prob. of Select Dose-over-MTD 0.02 0.024 0.027 0.126 0.068 0.079 0.077 Prob. of No Selection 0.002 0 0.009 Scenario 7 Target Toxicity Prob. = 0.17 Selection Prol # of Patients Treated # of Toxicities mTPI mTPI-2 BOIN BLRM CRM mTPI-2 BLRM CRM mTPI-2 BOIN BLRM CRM Dose Level i3+3 i3+3 mTP1 BOIN i3+3 mTPI True Tox Prob. 3+3 3+3 3+3 0.01 0.001 0 3 306 3 402 3 084 3 249 3.21 0 0.034 0.034 0.03 0 0.036 0.034 0.01 0.002 0.008 0.014 0.017 0.006 0.009 0.011 3.078 3.435 3.975 3.12 3.561 4.212 3.396 Λ 0.032 0.04 0.029 Ω 0.042 0.032 0.04 0.035 0.043 0.099 0.064 0.048 0.126 0.042 4.143 4.731 5.397 3.504 5.097 8.607 4.338 0.132 0.214 0.232 0.145 0.203 0.345 0.191 0.07 0.224 0.235 0.268 0.14 0.206 0.479 0.275 5,679 5.436 6.231 3.834 6.354 8.793 7.41 0.384 0.344 0.433 0.3 0.456 0.632 0.498 10.434 0.12 0.71 0.61 0.7460.738 0.356 0.651 11.223 8.661 5.322 9,498 3.879 1.361 1.28 1.052 0.642 1.072 0.455 1.126 0.67 0.001 0.004 0.009 0.029 0.002 0.021 0.021 2.877 2.658 2.334 2.934 2.49 1.017 2.367 1.894 1.803 1.562 1.972 1.675 0.685 1.604 i3+3 mTPI mTPI-2 3+3 BOIN BLRM CRM Prob. of Select MTD 0.738 0.71 0.61 0.746 0.738 0.356 0.651 Prob. of Toxicity 0.126 0.124 0.112 0.143 0.112 0.074 0.116 Prob. of Select Dose-over-MTD 0.001 0.004 0.009 0.029 0.002 0.021 0.021 Prob. of No Selection 0 0.003 0.009 0 Scenario 8 Target Toxicity Prob. = 0.17 Selection Prol # of Patients Treated # of Toxicities Dose Level True Tox Prob. i3+3 mTPI mTPI-2 3+3 BOIN BLRM CRM i3+3 mTPI mTPI-2 3+3 BOIN BLRM CRM i3+3 mTPI mTPI-2 3+3 BOIN BLRM CRM 0.291 0.399 0.203 0.248 11.928 11.901 15.285 4.49 13.077 9.639 12.231 1.938 2.449 1.495 1.965 0.31 2.061 0.198 0.193 0.185 0.174 0.229 0.251 0.219 6.762 7.458 6.189 3.603 7.971 6.516 1.186 1.333 1.127 0.655 1.205 1.456 1.173 0.18 6.78 0.2 0.143 0.156 0.107 0.146 0.15 0.148 0.183 4.125 4.194 3.234 2.754 3.753 4.398 4.758 0.828 0.819 0.628 0.556 0.72 0.848 0.901 0.22 0.08 0.088 0.058 0.085 0.077 0.051 0.101 2.364 2.22 1.449 1.884 1.869 1.101 2.436 0.537 0.492 0.313 0.439 0.412 0.251 0.539 0.24 0.06 0.04 0.024 0.076 0.0520.01 0.039 1.047 0.891 0.63 1.272 0.9 0.231 0.933 0.259 0.213 0.149 0.2910.1970.047 0.227 0.26 0.021 0.015 0.007 0.089 0.024 0.005 0.014 0.579 0.429 0.273 0.759 0.495 0.057 0.339 0.157 0.123 0.081 0.211 0.128 0.008 0.1 CRM i3+3 mTPI mTPI-2 3+3 BOIN BLRM Prob. of Select MTD 0.712 0.762 0.749 0.608 0.773 0.698 0.813 Prob. of Toxicity 0.175 0.183 0.181 0.175 0.195 0.176 0.18 Prob. of Select Dose-over-MTD 0.081 0.055 0.031 0.165 0.076 0.015 0.053 Prob. of No Selection 0.207 0.183 0.227 0.151 0.287 0.134 Scenario 9 Target Toxicity Prob. = 0.17 Selection Pro # of Patients Treated # of Toxicities Dose Level True Tox Prob. i3+3 mTPImTPI-2 3+3 BOIN BLRM CRM i3+3 mTPI mTPI-2 3+3 BOIN BLRM CRM i3+3 mTPI mTPI-2 3+3 BOIN BLRM CRM 0.196 0.142 0.224 0.155 0.19 9.285 10.005 12.327 4.191 10.686 9.531 1.164 0.519 1.253 0.907 1.152 1.189 0.19 0.201 0.224 0.148 0.224 0.266 0.234 6.834 7.638 7.302 3.726 8.52 7.239 0.9 1.079 1.053 1.011 1.182 1.008 7.122 0.513 0.201 0.209 5.295 5.208 4.311 3.189 4.983 6.405 0.684 0.921 0.16 0.187 0.167 0.15 0.196 0.232 5.589 0.815 0.846 0.508 0.758 1.009 0.18 0.149 0.145 0.095 0.122 0.117 0.124 0.165 3.582 3.165 2.496 2.568 2.913 2.301 3.576 0.64 0.577 0.44 0.48 0.516 0.41 0.62 0.067 0.083 2.043 1.623 1.296 2.007 0.441 0.334 0.252 0.283 0.1 0.349 0.2 0.063 0.104 0.103 0.03 1.569 1.686 0.408 0.413 0.115 0.22 0.067 0.064 0.038 0.185 0.064 0.005 0.047 1.488 1.026 0.753 1.278 1.002 0.09 0.804 0.351 0.221 0.171 0.304 0.213 0.026 0.174 BLRM i3+3 mTPI mTPI-2 3+3 BOIN CRM Prob. of Select MTD 0.904 0.924 0.906 0.851 0.928 0.812 0.928 Prob. of Toxicity 0.149 0.15 0.148 0.143 0.161 0.143 0.142 Prob. of Select Dose-over-MTD Prob. of No Selection 0.096 0.076 0.094 0.149 0.072 0.188 0.072 Scenario 10 Target Toxicity Prob. = 0.17 Selection Prol # of Patients Treated # of Toxicities Dose Level True Tox Prob. i3+3mTPI mTPI-2 3+3 BOIN BLRM CRM i3+3 mTPI mTPI-2 3+3 BOIN BLRM CRM i3+3 mTPI mTPI-2 3+3 BOIN BLRM CRM 0.179 0.075 0.082 0.054 0.083 6.78 9.39 3.834 7.404 5.649 6.927 0.528 0.589 0.735 0.336 0.568 0.443 0.559 0.1 0.157 0.171 0.226 0.125 0.171 0.213 0.184 6.759 7.266 7.542 3.765 6.984 8.229 6.663 0.703 0.723 0.787 0.352 0.672 0.765 0.672 0.166 0.224 0.125 0.213 0.298 0.236 5.454 5.76 3.585 5.718 8.265 6.639 0.642 0.635 0.463 0.667 0.971 0.798 0.12 0.2020.14 0.182 0.221 0.155 0.126 0.179 0.209 0.208 4.38 4.236 3.522 3.114 4.218 3.966 0.609 0.539 0.45 0.594 0.543 0.665 4.722 0.16 0.204 0.101 0.086 0.118 0.164 0.095 0.145 3.192 2.463 1.974 2.745 2.793 1.245 2.577 0.521 0.395 0.314 0.442 0.448 0.209 0.425 0.111 0.355 0.037 0.126 2.442 1.701 1.932 2.226 0.523 0.399 0.18 0.158 0.162 0.164 2.892 0.348 2.001 0.445 0.305 0.346 0.067 0.356 i3+3 mTPI mTPI-2 3+3 BOIN BLRM CRM Prob. of Select MTD 0.71 0.686 0.576 0.724 0.72 0.639 0.715 Prob. of Toxicity 0.12 0.117 0.112 0.126 0.114 0.108 0.118 Prob. of Select Dose-over-MTD Prob. of No Selection 0.021 0.018 0.019 0.076 0.027 0.094 0.018

Scenario 11 Target Toxicity Prob. = 0.17 # of Patients Treated # of Toxicities Selection Prob BLRM CRM BLRM CRM BLRM CRM mTPI-2 ROIN Dose Level True Tox Prob. i3 + 3mTPI mTPI-2 3+3 BOIN i3+3 mTPI mTPI-2 3+3 ROIN i3+3 mTPI 3+3 0.072 0.036 0.066 0.027 0.031 4.017 3.309 4.374 4.167 0.067 0.071 0.106 0.103 0.093 0.08 0.195 0.188 0.317 0.187 0.193 0.263 0.142 7.059 7.554 9.138 4.104 8.427 9.513 6.558 0.531 0.609 0.749 0.348 0.695 0.733 0.551 0.14 0.335 0.329 0.323 0.347 0.412 0.346 7.863 7.866 4.23 7.824 10.479 8.601 1.127 0.627 1.042 1.436 1.166 0.238 0.247 4.863 6.819 1.246 0.948 0.979 0.789 0.262 0.319 0.716 2.715 0.26 0.137 0.107 0.076 0.155 0.141 0.056 0.126 3.144 3.087 1.995 2.322 0.771 2.979 0.819 0.811 0.516 0.721 0.577 0.194 0.798 0.32 0.034 0.02 0.136 0.036 0.005 0.034 1.359 1.065 0.63 1.305 0.936 0.171 0.822 0.435 0.339 0.197 0.437 0.303 0.054 0.259 6 0.036 i3+3 mTPI mTPI-2 3+3 BOIN BLRM CRM Prob. of Select MTD 0.597 0.633 0.519 0.458 0.594 0.635 0.665 Prob. of Toxicity 0.141 0.139 0.122 0.15 0.124 0.111 0.138 Prob. of Select Dose-over-MTD 0.173 0.141 0.096 0.291 0.177 0.061 0.16 Prob. of No Selection 0.001 0.002 0.002 0.004 0.002 0.014 0.002 Scenario 12 Target Toxicity Prob. = 0.17 # of Patients Treated # of Toxicities Selection Prob i3+3 mTPI mTPI-2 BOIN BLRM CRM mTPI BOIN BLRM CRM i3+3 mTPI mTPI-2 BOIN BLRM CRM Dose Level True Tox Prob. 3+3 i3+3 mTPI-2 3+3 3+3 0.02 0.027 0.027 0.049 0.046 0.023 0.024 3.969 3.969 5.127 3.279 5.043 4.215 3.969 0.078 0.07 0.102 0.063 0.097 0.09 0.071 0.07 0.151 0.138 0.258 0.157 0.154 0.188 0.103 6 2 7 3 6.87 8 196 3 96 7.71 8 325 5 907 0.429 0.498 0.585 0.286 0.554 0.559 0.446 0.282 0.295 0.188 0.394 0.294 0.376 7.443 7.56 5.856 4.143 3.834 10.521 7.89 7.677 0.915 0.941 0.955 1.223 0.838 0.922 1.244 0.308 6.756 6.897 0.649 0.9430.27 0.152 0.126 0.086 0.187 0.171 0.069 0.172 3.87 3.882 2.514 3.105 2 901 1.098 3.657 1.063 1.057 0.686 0.848 0.754 0.297 1.014 0.34 0.042 0.036 0.024 0.134 0.035 0.009 0.029 1.662 1.188 0.693 1.425 1.065 0.18 0.846 0.554 0.41 0.237 0.51 0.353 0.058 0.292 i3+3 mTPI mTPI-2 3+3 BOIN BLRM CRM Prob. of Select MTD 0.627 0.671 0.581 0.469 0.612 0.697 0.67 Prob. of Toxicity 0.139 0.135 0.117 0.148 0.12 0.103 0.133 Prob. of Select Dose-over-MTD 0 194 0.162 0.11 0.321 0.206 0.078 0.201 Prob. of No Selection 0.002 0.007 0.002 0.014 0.002 0.001 0.002 Scenario 13 Target Toxicity Prob. = 0.17 Selection Pro # of Patients Treated # of Toxicities Dose Level True Tox Prob. i3+3 mTPI mTPI-2 3+3 BOIN BLRM CRM mTPI mTPI-2 3+3 BOIN BLRM CRM mTPI mTPI-2 3+3 BOIN BLRM CRM 0.404 0.404 0.47 0.266 0.441 0.298 0.394 13.401 4.686 15.072 10.566 13.311 2.215 2.134 0.8 2.496 2.243 16,626 2.801 1.718 0.223 0.229 0.231 0.236 0.277 3.792 7.908 1.387 0.178 7.683 8.265 6.288 1.714 1.814 0.851 1.561 1.688 1.68 0.27 0.099 0.105 0.061 0.145 0.116 0.094 0.117 3.855 3.663 2.499 2.505 3.054 3.27 3.882 1.031 1.004 0.667 0.695 0.822 0.837 1.029 0.32 0.039 0.029 0.015 0.073 0.038 0.008 0.032 1.419 1.278 0.735 1.365 1.101 0.477 1.317 0.471 0.416 0.245 0.44 0.345 0.151 0.403 0.37 0.008 0.008 0.002 0.002 0.008 0.321 0.174 0.059 0.242 0.113 5 0.025 0.004 0.432 0.639 0.285 0.027 0.267 0.158 0.112 0.008 0.099 0.42 Λ Λ Λ 0.013 Ω Λ Λ 0.078 0.057 0.033 0.165 0.042 0.012 0.048 0.04 0.028 0.014 0.07 0.015 0.005 0.024 i3+3 mTPI mTPI-2 3+3 BOIN BLRM CRM Prob. of Select MTD 0.677 0.671 0.627 0.633 0.648 0.497 0.55 Prob. of Toxicity 0.21 0.209 0.196 0.236 0.2 0.198 0.207 Prob. of Select Dose-over-MTD 0.078 0.256 0.158 0.146 0.142 0.104 0.157 Prob. of No Selection 0.227 0.225 0.274 0.247 0.165 0.346 0.172 Scenario 14 Target Toxicity Prob. = 0.17 Selection Prol # of Patients Treated # of Toxicities Dose Level True Tox Prob. i3+3 mTPI mTPI-2 3+3 BOIN BLRM CRM mTPI mTPI-2 3+3 BOIN BLRM CRM i3 + 3mTPI mTPI-2 3+3 BOIN BLRM CRM 0.02 0.01 0.012 0.015 0.024 0.014 0.008 0.011 3 744 3.72 4.416 3 207 4 488 3.843 3.636 0.083 0.066 0.084 0.058 0.087 0.085 0.066 0.05 0.053 0.044 0.11 0.06 0.074 0.081 0.036 4.653 5.22 6.111 3.54 5.952 6.405 4.464 0.214 0.275 0.311 0.18 0.324 0.308 0.238 0.08 0.119 0.147 0.204 0.109 0.157 0.256 0.143 5.691 5.784 6.39 3.876 6.135 9.354 6.183 0.441 0.428 0.498 0.326 0.482 0.674 0.457 4 0.11 0.275 0.257 0.128 0.241 0.338 0.277 5.76 5.637 3.798 5.454 6.633 0.618 0.615 0.579 0.677 0.709 0.2 5.616 6.618 0.614 0.441 0.14 0.198 0.199 0.256 4.749 4.68 4.101 3.504 3.954 2.499 4.881 0.624 0.601 0.475 0.536 0.288 0.199 0.153 0.23 0.696 0.347 0.33 0.321 0.214 0.518 0.282 0.104 0.275 5.547 4.782 3.291 2.709 3.963 0.894 0.954 0.567 0.473 0.719 4.164 0.809 0.638 0.146 BLRM i3+3 mTPI mTPI-2 3+3 ROIN CRM Prob. of Select MTD 0.618 0.52 0.412 0.671 0.512 0.303 0.531 Prob. of Toxicity 0.098 0.096 0.089 0.095 0.088 0.076 0.096

Prob. of Select Dose-over-MTD

Prob. of No Selection

0

0.002

0.008

0.002

0

0.002

0.014

0.002

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Scen	ario	ı

Transfer Frok - 0.5 Decision From Prof.
1
2
3 0.1 0.15 0.15 0.15 0.25 0.25 0.25 0.25 0.25 0.25 0.25 0.2
4
Column C
Prob. of Scient HTD
Pack of Science Pack of Sc
Prob. of Trainising 1.64
Prob. of Sicket Dase-serve HID 0 0 0 0 0 0 0 0 0
Prob. of No Schedum
Target Toxicisy Posh - 0.3 13.1 mTP Target Selection Prob. 13.2 mTP
Figure Transport Transpo
Doctor Time Tay Prob. 13-3 mTP mTP 2 3-3 BON BIRM CRM 13-4 Time Tim
1
3 0.5 0.018 0.013 0.02 0.01 0.026 0.011 0.027 1.08 0.033 1.011 0.459 1.212 0.72 1.08 0.554 0.476 0.517 0.233 0.92 0.377 0.344 0.6 0.001 0 0.001 0 0.001 0 0.001 0 0.001 0 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0000 0.0
4 0.6 0.00 0 0 0.001 0 0.004 0 0 0 0.15 0.14 0.18 0.099 0.21 0.087 0.309 0.092 0.075 0.088 0.046 0.116 0.048 0.195 0.007 0.00 0 0 0 0 0 0 0 0 0 0 0 0 0 0
5 0.7 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
Column C
Prob. of Select MTD
Prob. of Select MTD Prob. of Toxicity Prob. of T
Prob. of Toxicity Prob. of Toxicity Prob. of Select Dose-over-MTD O.15% O.1 O.16% O.10%
Prob. of Selection 0.463 0.45
Prob. of No Selection No
Section Prob. Section Prob
Traget T
1 0.01 0.319 0.309 0.333 0.604 0.164 0.217 0.184 7.737 6.573 8.259 4.839 8.043 7.257 7.212 0.065 0.009 0.087 0.047 0.075 0.071 0.071 0.071 0.071 0.073 0.075
2 0.3 0.636 0.656 0.627 0.388 0.753 0.747 0.73 1.6647 18.315 16.524 5.233 16.572 17.859 15.114 4.919 5.448 4.916 1.622 4.918 5.336 4.512 3.0033 0.037 0.036 0.037 0.036 0.008 0.008 0.008 0.008 0.0002 0.002 0.003 0.002 0.004 0 0 0 0.056 5.088 4.737 4.848 2.049 4.974 4.551 6.666 2.797 2.63 2.673 0.234 0.142 0.258 0.196 0.636 5.088 0.002 0.002 0.003 0.002 0.004 0 0 0 0.056 0.357 0.363 0.258 0.396 0.315 0.945 0.329 0.23 0.234 0.174 0.258 0.196 0.636 6 0.95 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
3 0.55 0.43 0.033 0.037 0.036 0.079 0.036 0.079 0.036 0.086 5.088 4.737 4.836 2.049 4.974 4.551 6.66 2.797 2.63 2.673 1.121 2.737 2.554 3.664 5.002 0.002 0.002 0.002 0.002 0.002 0.002 0.002 0.002 0.002 0.003 0.002 0.003 0.002 0.003 0.002 0.003 0.002 0.003 0.002 0.003 0.003 0.003 0.003 0.003 0.003 0.003 0.003 0.003 0.004 0.005 0.008 0.015 0.015 0.018 0.069 0.008 0.012 0.011 0.014 0.016 0.053 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.005 0.008 0.002 0.001 0.014 0.016 0.053 0.005 0.
4 0.65 0.002 0.002 0.003 0.002 0.004 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
5 0.8 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
6 0.95 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
Select MTD
Prob. of Select MTD 0.66 0.656 0.627 0.288 0.264 0.24 0.267 0.272 0.298 Prob. of Toxicity Prob. of Selection 0 0 0 0 0 0 0 0 0
Prob. of Selection Prob. of No Selection Pro
Prob. of No Selection Companies Comp
Scenario 4 Target Toxicity Prob. = 0.3 Dose Level True Tox Prob. i3+3 mTPI mTPI-2 3+3 BOIN BLRM CRM CRM i3+3 mTPI mTPI-2 3+3 BOIN BLRM CRM
Target Toxicity Prob. = 0.3 Selection Prob. 3+3 MTPI MTPI-2 3+3 BOIN BLRM CRM 13+3 MTPI MTPI MTPI MTPI-2 3+3 BOIN BLRM CRM 13+3 MTPI MTPI MTPI MTPI-2 3+3 BOIN BLRM CRM 13+3 MTPI MTTI MTPI MTTI MTPI MTPI MTTI MT
Dose Level True Tox Prob. 13+3 mTPI mTPI-2 3+3 BOIN BLRM CRM CRM 13+3 mTPI mTPI-2 3+3 BOIN BLRM CRM CRM 13+3 mTPI mTPI-2 3+3 BOIN BLRM CRM CR
1 0.04 0.002 0.001 0.001 0.031 0 0 0.001 3.492 3.558 3.522 3.414 3.438 3.303 3.474 0.139 0.152 0.149 0.133 0.128 0.12 0.148 2 0.06 0.003 0.002 0.003 0.064 0.003 0.002 0.002 3.858 3.927 3.807 3.591 3.864 3.642 3.162 0.249 0.242 0.242 0.242 0.211 0.238 0.173 0.197 3.008 0.011 0.022 0.011 0.089 0.011 0.028 0.01 4.185 4.431 4.161 3.687 4.17 5.178 3.6 0.356 0.37 0.341 0.305 0.343 0.414 0.303 0.44 0.303 0.304 0.323 0.304 0.323 0.436 0.197 0.337 0.214 0.348 5.739 0.279 4.422 0.393 8.208 0.09 0.615 0.57 0.622 0.456 0.61 0.777 0.607 0.00
2 0.06 0.003 0.002 0.003 0.064 0.003 0.002 0.003 0.064 0.003 0.002 0.002 3.858 3.927 3.807 3.591 3.864 3.642 3.162 0.249 0.242 0.242 0.211 0.238 0.173 0.197 0.1000 0.001 0.002 0.011 0.0029 0.0029
3 0.08 0.01 0.022 0.011 0.089 0.011 0.028 0.01 4.185 4.431 4.161 3.687 4.17 5.178 3.6 0.356 0.37 0.341 0.305 0.343 0.414 0.303 4.10 0.323 0.304 0.323 0.304 0.323 0.436 0.197 0.337 0.214 6.348 5.739 6.279 4.422 6.393 8.208 6.09 0.615 0.57 0.622 0.456 0.61 0.777 0.607 5.007 0.0
4 0.1 0.323 0.304 0.323 0.436 0.197 0.337 0.214 6.348 5.739 6.279 4.422 6.393 8.208 6.09 0.615 0.57 0.622 0.456 0.61 0.777 0.607 5 0.33 0.616 0.626 0.614 0.324 0.696 0.538 0.697 9.123 9.372 9.078 4.224 9.081 7.158 9.87 2.734 2.75 2.655 1.228 2.717 2.161 2.899 0.615 0.608 0.60
6 0.6 0.64 0.045 0.045 0.048 0.038 0.093 0.09 0.076 2.994 2.973 3.153 1.578 3.054 2.379 3.804 1.797 1.773 1.886 0.967 1.807 1.437 2.293 1.
13+3 mTPl mTPl-2 3+3 BOIN BLRM CRM
Prob. of Select MTD 0.616 0.626 0.614 0.324 0.696 0.538 0.697 Prob. of Toxicity 0.196 0.195 0.197 0.158 0.195 0.17 0.215 Prob. of Select Dose-over-MTD 0.045 0.045 0.048 0.038 0.093 0.09 0.076 Prob. of No Selection 0 0 0.018 0 0.005 0 Scenario 5 Target Toxicity Prob. = 0.3 Selection Prob. # of Patients Treated # of Toxicities
Prob. of Toxicity 0.196 0.195 0.197 0.158 0.195 0.17 0.215 Prob. of Select Dose-over-MTD 0.045 0.045 0.048 0.038 0.093 0.09 0.076 Prob. of No Selection 0 0 0.018 0 0.005 0 Scenario 5 Target Toxicity Prob. = 0.3 Selection Prob. # of Patients Treated # of Toxicities
Prob. of Select Dose-over-MTD 0.045 0.045 0.048 0.038 0.093 0.09 0.076 Prob. of No Selection 0 0 0 0.018 0 0.005 0 Scenario 5 Target Toxicity Prob. = 0.3 Selection Prob. # of Patients Treated # of Patients Treated
Prob. of No Selection 0 0 0.018 0 0.005 0 Scenario 5 Target Toxicity Prob. = 0.3 Selection Prob. # of Patients Treated # of Toxicities
Scenario 5 Target Toxicity Prob. = 0.3 Selection Prob. # of Patients Treated # of Toxicities
Target Toxicity Prob. = 0.3 Selection Prob. # of Patients Treated # of Toxicities
mile of Dam Beam Cam
1 0.05 0.99 0.99 0.982 0.929 0.886 0.93 0.919 21.477 20.826 21.345 5.88 20.922 20.937 20.436 1.075 1.102 1.114 0.287 1.005 1.011 1.052
2 0.6 0.009 0.009 0.017 0.042 0.114 0.049 0.08 8.121 8.739 8.226 3.924 8.682 7.842 8.199 4.884 5.258 4.943 2.4 5.155 4.73 4.915
3 0.8 0 0 0 0 0 0 0 0.402 0.411 0.405 0.255 0.396 0.72 1.317 0.319 0.327 0.321 0.197 0.315 0.569 1.057
4 0.9 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
6 0.99 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
6 0.99 i3+3 mTPI mTPI-2 3+3 BOIN BLRM CRM
Prob. of Select MTD 0.991 0.992 0.982 0.929 0.886 0.93 0.919
Prob. of Toxicity 0.209 0.223 0.213 0.287 0.216 0.214 0.235
Prob. of Select Dose-over-MTD 0.009 0.009 0.017 0.042 0.114 0.049 0.08
Prob. of No Selection 0 0.001 0.001 0.029 0 0.021 0.001

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Scenario 6 Target Toxicity Prob. = 0.3	11			Selection Prol	L			11		# ~6	Patients Tr							# of Toxicities			
Dose Level True Tox Prob.	i3+3	mTPI	mTPI-2	3+3	BOIN	BLRM	CRM	i3+3	mTPI	mTPI-2	3+3	BOIN	BLRM	CRM	i3+3	mTPI	mTPI-2	3+3	BOIN	BLRM	CRM
1 0.01	0.001	0.001	0.001	0.025	0	0.012	0.001	3.144	3.147	3.147	3.153	3.102	3.132	3.129	0.032	0.034	0.034	0.03	0.023	0.036	0.034
2 0.05	0.003	0.003	0.006	0.126	0.005	0.003	0.006	3.732	3.75	3.732	3.765	3.819	3.789	3.258	0.201	0.177	0.178	0.191	0.196	0.17	0.151
3 0.1	0.963	0.952	0.96	0.814	0.826	0.845	0.878	15.45	14.934	15.357	5.685	15.414	16.728	14.763	1.488	1.53	1.566	0.602	1.49	1.616	1.517
4 0.6	0.033	0.042	0.032	0.032	0.169	0.14	0.114	7.254	7.719	7.35	3.495	7.335	6.024	7.737	4.382	4.605	4.403	2.121	4.388	3.624	4.627
5 0.7	0	0.002	0.001	0.001	0	0	0.001	0.405	0.435	0.399	0.237	0.324	0.318	1.062	0.29	0.299	0.277	0.164	0.238	0.228	0.769
6 0.9	0	0	0	0	0	0	0	0.015	0.015	0.015	0.006	0.006	0.009	0.051	0.015	0.012	0.012	0.005	0.005	0.009	0.04
D 1 00 1 11 11 11 11 11 11 11 11 11 11 11	i3+3	mTPI	mTPI-2	3+3	BOIN	BLRM	CRM														
Prob. of Select MTD Prob. of Toxicity	0.963	0.952	0.96	0.814	0.826	0.845	0.878														
Prob. of Select Dose-over-MTD	0.214 0.033	0.222 0.044	0.216 0.033	0.191 0.033	0.211 0.169	0.189 0.14	0.238 0.115														
Prob. of No Selection	0.033	0.044	0.055	0.033	0.169	0.14	0.113														
Scenario 7		v	Ü	0.002	Ü	Ü	v	<u>II</u>													Ī
Target Toxicity Prob. = 0.3			S	Selection Prol	b.					# of	Patients Tre	eated						# of Toxicities	;		
Dose Level True Tox Prob.	i3+3	mTPI	mTPI-2	3+3	BOIN	BLRM	CRM	i3+3	mTPI	mTPI-2	3+3	BOIN	BLRM	CRM	i3+3	mTPI	mTPI-2	3+3	BOIN	BLRM	CRM
1 0.01	0	0.001	0.001	0.011	0	0	0.001	3.132	3.132	3.126	3.114	3.075	3.102	3.129	0.04	0.034	0.034	0.033	0.023	0.036	0.034
2 0.03	0.001	0	0	0.051	0.001	0.002	0.001	3.399	3.327	3.321	3.408	3.387	3.399	3.027	0.11	0.084	0.083	0.111	0.1	0.099	0.07
3 0.07	0.007	0.015	0.009	0.092	0.005	0.014	0.002	4.032	4.248	4.041	3.828	4.005	4.83	3.231	0.295	0.317	0.303	0.292	0.289	0.321	0.259
4 0.1	0.061	0.079	0.058	0.187	0.031	0.187	0.034	4.692	4.728	4.671	3.942	4.704	6.966	4.08	0.454	0.455	0.45	0.399	0.465	0.639	0.404
5 0.15 6 0.75	0.913 0.018	0.891 0.014	0.92 0.012	0.648 0.007	0.922 0.041	0.712 0.085	0.92 0.042	10.554 4.191	10.761 3.804	10.839 4.002	4.884 2.37	10.707 4.122	8.373 3.33	12.159 4.374	1.602 3.068	1.6 2.854	1.612 3.001	0.748 1.788	1.583 3.089	1.237 2.487	1.779 3.291
0.73	i3+3	mTPI	mTPI-2	3+3	BOIN	BLRM	CRM	7.171	3.004	7.002	2.31	7.122	5.55	7.3/4	3.000	4.034	5.001	1./00	3.007	4.70/	3.471
Prob. of Select MTD	0.913	0.891	0.92	0.648	0.922	0.712	0.92														
Prob. of Toxicity	0.186	0.178	0.183	0.156	0.185	0.161	0.195														
Prob. of Select Dose-over-MTD	0.018	0.014	0.012	0.007	0.041	0.085	0.042														
Prob. of No Selection	0	0	0	0.004	0	0	0														
Scenario 8	ıı										n .:										
Target Toxicity Prob. = 0.3	i3+3	TDI		Selection Prol 3+3	b. BOIN	DIDM	CRM	i3+3	mTPI		Patients Tro 3+3	eated BOIN	BLRM	CRM	i3+3	TDI		# of Toxicities 3+3	BOIN	BLRM	CRM
Dose Level True Tox Prob.	0.351	mTPI 0.38	mTPI-2 0.346	0.256	0.356	BLRM 0.22	0.344	14.202	14.883	mTPI-2 14.487	4.968	14.16	9.213	13,362	4.038	mTPI 4.274	mTPI-2 4.164	1.421	4.101	2.694	3.895
2 0.31	0.197	0.199	0.185	0.118	0.224	0.236	0.2	7.164	7.119	7.044	2.595	6.894	7.716	6.282	2.289	2.236	2.201	0.834	2.104	2.344	1.945
3 0.33	0.118	0.123	0.144	0.07	0.131	0.124	0.182	3.315	3.435	3.588	1.182	3.597	3.645	4.557	1.087	1.073	1.136	0.383	1.182	1.193	1.443
4 0.35	0.063	0.052	0.07	0.017	0.079	0.038	0.091	1.41	1.284	1.56	0.558	1.611	1.017	2.166	0.495	0.456	0.558	0.22	0.557	0.36	0.75
5 0.37	0.028	0.027	0.026	0.005	0.036	0.009	0.038	0.498	0.426	0.477	0.171	0.588	0.243	0.801	0.186	0.157	0.172	0.064	0.212	0.08	0.302
6 0.39	0.014	0.007	0.016	0.005	0.017	0.014	0.008	0.123	0.102	0.159	0.045	0.195	0.132	0.177	0.046	0.048	0.066	0.016	0.076	0.046	0.079
	i3+3	mTPI	mTPI-2	3+3	BOIN	BLRM	CRM														
Prob. of Select MTD	0.729	0.754	0.745	0.461	0.79	0.618	0.817														
Prob. of Toxicity Prob. of Select Dose-over-MTD	0.305 0.042	0.303 0.034	0.304 0.042	0.309 0.01	0.304 0.053	0.306 0.023	0.308 0.046														
Prob. of No Selection	0.042	0.034	0.042	0.529	0.055	0.023	0.046														
Scenario 9	0.229	0.212	0.213	0.329	0.137	0.339	0.137	Į							Į						J
Target Toxicity Prob. = 0.3			S	Selection Prol	b.			l		# of	Patients Tr	eated			l			# of Toxicities	;		
Dose Level True Tox Prob.	i3+3	mTPI	mTPI-2	3+3	BOIN	BLRM	CRM	i3+3	mTPI	mTPI-2	3+3	BOIN	BLRM	CRM	i3+3	mTPI	mTPI-2	3+3	BOIN	BLRM	CRM
1 0.25	0.27	0.329	0.286	0.247	0.256	0.209	0.218	12.093	13.023	12.438	4.872	11.829	9.207	11.019	3.015	3.198	3.031	1.229	2.888	2.266	2.708
2 0.27	0.219	0.252	0.23	0.161	0.217	0.273	0.258	7.749	8.34	7.914	2.925	7.71	8.361	7.275	2.079	2.311	2.209	0.809	2.095	2.282	1.999
3 0.29	0.166	0.152	0.164	0.077	0.2	0.165	0.204	4.464	4.11	4.431	1.623	4.737	4.749	5.235	1.272	1.169	1.282	0.496	1.365	1.428	1.514
4 0.31 5 0.33	0.125 0.065	0.086 0.042	0.108 0.058	0.037 0.016	0.126 0.071	0.078 0.03	0.141 0.069	2.415	1.809 0.738	2.151 1.029	0.78 0.36	2.37 1.137	1.758 0.489	3.111 1.209	0.751 0.335	0.551 0.23	0.655 0.328	0.258 0.12	0.723 0.365	0.546 0.15	0.948 0.388
6 0.35	0.003	0.042	0.038	0.018	0.071	0.03	0.033	0.948 0.351	0.756	0.441	0.36	0.501	0.489	0.555	0.333	0.23	0.328	0.12	0.363	0.13	0.388
0.33	i3+3	mTPI	mTPI-2	3+3	BOIN	BLRM	CRM	0.551	0.554	0.771	0.155	0.501	0.21)	0.555	0.133	0.124	0.170	0.03	0.107	0.070	0.100
Prob. of Select MTD	0.874	0.889	0.891	0.551	0.914	0.775	0.923														
Prob. of Toxicity	0.271	0.267	0.269	0.277	0.27	0.272	0.273								1						
Prob. of Select Dose-over-MTD	0	0	0	0	0	0	0														
Prob. of No Selection	0.126	0.111	0.109	0.449	0.086	0.225	0.077														l
Scenario 10			_																		
Target Toxicity Prob. = 0.3		TDI		Selection Prol		DIDM	CDM		TDI		Patients Tr		DIDM	CDM		TDI		# of Toxicities		DIDIG	CDM
Dose Level True Tox Prob.	i3+3 0.158	mTPI	mTPI-2	3+3 0.244	BOIN	BLRM	CRM 0.126	i3+3	mTPI	mTPI-2	3+3 4.767	BOIN	BLRM 7.551	CRM 8.622	i3+3	mTPI	mTPI-2	3+3 1.027	BOIN	BLRM	CRM
1 0.21 2 0.23	0.158	0.218 0.247	0.163 0.209	0.244	0.151 0.202	0.14 0.232	0.126	9.444 7.551	10.587 8.31	9.552 7.851	4.767 3.27	9.564 7.596	7.551 8.271	6.879	1.95 1.715	2.161 1.925	1.967 1.799	0.788	1.983 1.699	1.539 1.927	1.765 1.602
3 0.25	0.203	0.247	0.209	0.155	0.202	0.232	0.21	5.616	5.361	5.706	2.031	5.643	6.288	6.231	1.713	1.925	1.799	0.788	1.699	1.552	1.602
4 0.27	0.179	0.138	0.152	0.072	0.204	0.148	0.233	3.561	2.811	3.411	1.281	3.618	2.856	4.044	0.981	0.767	0.939	0.493	0.979	0.802	1.087
5 0.29	0.107	0.071	0.124	0.031	0.127	0.058	0.133	1.797	1.338	1.68	0.696	1.8	0.981	2.205	0.548	0.39	0.469	0.214	0.512	0.288	0.63
6 0.31	0.089	0.067	0.09	0.034	0.109	0.049	0.078	0.912	0.783	0.99	0.288	1.089	0.624	1.209	0.297	0.241	0.313	0.088	0.362	0.213	0.364
	i3+3	mTPI	mTPI-2	3+3	BOIN	BLRM	CRM														
Prob. of Select MTD	0.574	0.487	0.581	0.247	0.614	0.486	0.629														
Prob. of Toxicity Prob. of Select Dose-over-MTD	0.239	0.234	0.237	0.24	0.237	0.238	0.241														
Prob. of No Selection	0 0.065	0 0.048	0 0.047	0 0.356	0 0.033	0 0.142	0 0.035														
1100. of No Belection	0.005	0.070	0.077	0.550	0.055	0.172	0.055	II													l

Scenario 11

Scenario 11																					
Target Toxicity Prob. = 0.3			S	election Prob	b.					# of	Patients Tre	eated					;	# of Toxicities	S		
Dose Level True Tox Prob.	i3+3	mTPI	mTPI-2	3+3	BOIN	BLRM	CRM	i3+3	mTPI	mTPI-2	3+3	BOIN	BLRM	CRM	i3+3	mTPI	mTPI-2	3+3	BOIN	BLRM	CRM
1 0.05	0.067	0.057	0.071	0.328	0.042	0.032	0.043	4.986	4.641	5.16	4.269	5.085	4.434	4.521	0.236	0.243	0.263	0.199	0.244	0.189	0.233
2 0.2	0.274	0.276	0.252	0.298	0.207	0.309	0.163	9,543	9,933	9.273	4.761	9.183	9,969	6.66	1.947	2.013	1.89	0.986	1.812	1.969	1.374
3 0.27	0.329	0.338	0.309	0.204	0.352	0.4	0.318	8.466	8.529	8.064	3.366	8.265	9.807	8.763	2.337	2.259	2.141	0.91	2.208	2.679	2.408
4 0.33	0.196	0.228	0.232	0.107	0.243	0.185	0.309	4.704	4.548	4.848	1.932	4.995	4.221	6.201	1.589	1.469	1.562	0.639	1.656	1.385	1.979
5 0.39	0.190						0.309	1.734					1.149	2,964				0.039	0.735	0.452	1.126
		0.079	0.101	0.035	0.116	0.051			1.911	2.097	0.831	1.968			0.66	0.745	0.826				
6 0.45	0.035	0.021	0.034	0.004	0.04	0.017	0.03	0.567	0.42	0.54	0.24	0.504	0.261	0.891	0.243	0.191	0.241	0.121	0.229	0.123	0.413
	i3+3	mTPI	mTPI-2	3+3	BOIN	BLRM	CRM														
Prob. of Select MTD	0.525	0.566	0.541	0.311	0.595	0.585	0.627														
Prob. of Toxicity	0.234	0.231	0.231	0.207	0.229	0.228	0.251														
Prob. of Select Dose-over-MTD	0.134	0.1	0.135	0.039	0.156	0.068	0.167														
Prob. of No Selection	0	0.001	0.001	0.024	0	0.006	0														
Scenario 12		0.001	0.001	0.02	Ü	0.000	0														J
Target Toxicity Prob. = 0.3	II		C.	election Prob	h					# of	Patients Tre	natad						# of Toxicities			
	:2.12				BOIN	BLRM	CRM	:2.12	TDI				DIDM	CRM	:2 2	mTPI				DIDM	CDM
Dose Level True Tox Prob.	i3+3	mTPI	mTPI-2	3+3				i3+3	mTPI	mTPI-2	3+3	BOIN	BLRM		i3+3		mTPI-2	3+3	BOIN	BLRM	CRM
1 0.05	0.007	0.004	0.005	0.087	0.002	0.001	0.004	3.864	3.834	3.81	3.615	3.711	3.477	3.693	0.21	0.201	0.2	0.188	0.178	0.147	0.195
2 0.1	0.071	0.068	0.072	0.29	0.04	0.086	0.034	5.517	5.55	5.562	4.392	5.604	5.802	4.053	0.555	0.565	0.571	0.43	0.552	0.54	0.422
3 0.2	0.337	0.382	0.354	0.308	0.297	0.408	0.237	8.346	9.312	8.793	4.428	8.583	10.845	7.368	1.625	1.893	1.743	0.912	1.664	2.22	1.483
4 0.3	0.362	0.373	0.357	0.218	0.406	0.383	0.455	7.764	7.425	7.536	3.153	7.752	7.119	8.883	2.341	2.212	2.269	0.93	2.321	2.119	2.61
5 0.4	0.146	0.144	0.17	0.053	0.173	0.098	0.232	3.42	3.132	3.384	1.53	3.333	2.133	4.68	1.376	1.24	1.347	0.629	1.317	0.89	1.869
6 0.5	0.077	0.029	0.042	0.012	0.082	0.018	0.038	1.089	0.747	0.915	0.366	1.017	0.465	1.323	0.421	0.356	0.452	0.199	0.393	0.235	0.665
0.5	i3+3	mTPI	mTPI-2	3+3	BOIN	BLRM	CRM	1.005	0.7.7	0.515	0.500	1.017	005	1.525	0.121	0.550	02	0.177	0.575	0.235	0.005
Prob. of Select MTD	0.362	0.373	0.357	0.218	0.406	0.383	0.455														
Prob. of Toxicity	0.302	0.216	0.219	0.188	0.214	0.206	0.433														
	0.218																				
Prob. of Select Dose-over-MTD		0.173	0.212	0.065	0.255	0.116	0.27														
Prob. of No Selection	0	0	0	0.032	0	0.006	0														
Scenario 13																					
Target Toxicity Prob. = 0.3			S	election Prob	b.					# of	Patients Tre	eated						# of Toxicities	S		
Dose Level True Tox Prob.	i3+3	mTPI	mTPI-2	3+3	BOIN	BLRM	CRM	i3+3	mTPI	mTPI-2	3+3	BOIN	BLRM	CRM	i3+3	mTPI	mTPI-2	3+3	BOIN	BLRM	CRM
1 0.3	0.447		0.408	0.288	0.447	0.297	0.421	16.26	15.867	15.981	5.055	15.576	10.725	14.733		4.754				3.284	4.41
1 0.3	0.447	0.427	0.408	0.288	0.447	0.297	0.421	16.26 6.717	15.867 7.653	15.981 7.263	5.055 2.469	15.576 7.443	10.725 6.855	14.733	4.939	4.754 2.655	4.779	1.488	4.592	3.284 2.454	4.41 2.401
2 0.35	0.168	0.427 0.225	0.214	0.105	0.247	0.199	0.258	6.717	7.653	7.263	2.469	7.443	6.855	6.906	4.939 2.406	2.655	4.779 2.532	1.488 0.894	4.592 2.604	2.454	2.401
2 0.35 3 0.4	0.168 0.091	0.427 0.225 0.069	0.214 0.103	0.105 0.042	0.247 0.099	0.199 0.068	0.258 0.119	6.717 2.619	7.653 2.592	7.263 2.898	2.469 0.918	7.443 2.73	6.855 2.496	6.906 3.9	4.939 2.406 1.01	2.655 1.031	4.779 2.532 1.129	1.488 0.894 0.37	4.592 2.604 1.107	2.454 0.999	2.401 1.53
2 0.35 3 0.4 4 0.45	0.168 0.091 0.023	0.427 0.225 0.069 0.02	0.214 0.103 0.021	0.105 0.042 0.008	0.247 0.099 0.028	0.199 0.068 0.009	0.258 0.119 0.034	6.717 2.619 0.768	7.653 2.592 0.657	7.263 2.898 0.768	2.469 0.918 0.291	7.443 2.73 0.828	6.855 2.496 0.492	6.906 3.9 1.125	4.939 2.406 1.01 0.344	2.655 1.031 0.295	4.779 2.532 1.129 0.369	1.488 0.894 0.37 0.139	4.592 2.604 1.107 0.362	2.454 0.999 0.218	2.401 1.53 0.533
2 0.35 3 0.4 4 0.45 5 0.5	0.168 0.091 0.023 0.006	0.427 0.225 0.069 0.02 0.001	0.214 0.103 0.021 0.002	0.105 0.042 0.008 0.001	0.247 0.099 0.028 0.01	0.199 0.068 0.009 0.003	0.258 0.119 0.034 0.003	6.717 2.619 0.768 0.168	7.653 2.592 0.657 0.117	7.263 2.898 0.768 0.12	2.469 0.918 0.291 0.051	7.443 2.73 0.828 0.189	6.855 2.496 0.492 0.096	6.906 3.9 1.125 0.267	4.939 2.406 1.01 0.344 0.077	2.655 1.031 0.295 0.068	4.779 2.532 1.129 0.369 0.062	1.488 0.894 0.37 0.139 0.026	4.592 2.604 1.107 0.362 0.086	2.454 0.999 0.218 0.05	2.401 1.53 0.533 0.133
2 0.35 3 0.4 4 0.45	0.168 0.091 0.023 0.006 0.002	0.427 0.225 0.069 0.02 0.001 0	0.214 0.103 0.021 0.002 0	0.105 0.042 0.008 0.001 0	0.247 0.099 0.028 0.01 0	0.199 0.068 0.009 0.003 0	0.258 0.119 0.034 0.003 0	6.717 2.619 0.768	7.653 2.592 0.657	7.263 2.898 0.768	2.469 0.918 0.291	7.443 2.73 0.828	6.855 2.496 0.492	6.906 3.9 1.125	4.939 2.406 1.01 0.344	2.655 1.031 0.295	4.779 2.532 1.129 0.369	1.488 0.894 0.37 0.139	4.592 2.604 1.107 0.362	2.454 0.999 0.218	2.401 1.53 0.533
2 0.35 3 0.4 4 0.45 5 0.5 6 0.55	0.168 0.091 0.023 0.006 0.002 i3+3	0.427 0.225 0.069 0.02 0.001 0 mTPI	0.214 0.103 0.021 0.002 0 mTPI-2	0.105 0.042 0.008 0.001 0 3+3	0.247 0.099 0.028 0.01 0 BOIN	0.199 0.068 0.009 0.003 0 BLRM	0.258 0.119 0.034 0.003 0 CRM	6.717 2.619 0.768 0.168	7.653 2.592 0.657 0.117	7.263 2.898 0.768 0.12	2.469 0.918 0.291 0.051	7.443 2.73 0.828 0.189	6.855 2.496 0.492 0.096	6.906 3.9 1.125 0.267	4.939 2.406 1.01 0.344 0.077	2.655 1.031 0.295 0.068	4.779 2.532 1.129 0.369 0.062	1.488 0.894 0.37 0.139 0.026	4.592 2.604 1.107 0.362 0.086	2.454 0.999 0.218 0.05	2.401 1.53 0.533 0.133
2 0.35 3 0.4 4 0.45 5 0.5 6 0.55 Prob. of Select MTD	0.168 0.091 0.023 0.006 0.002 i3+3 0.615	0.427 0.225 0.069 0.02 0.001 0 mTPI 0.652	0.214 0.103 0.021 0.002 0 mTPI-2 0.622	0.105 0.042 0.008 0.001 0 3+3 0.393	0.247 0.099 0.028 0.01 0 BOIN 0.694	0.199 0.068 0.009 0.003 0 BLRM 0.496	0.258 0.119 0.034 0.003 0 CRM 0.679	6.717 2.619 0.768 0.168	7.653 2.592 0.657 0.117	7.263 2.898 0.768 0.12	2.469 0.918 0.291 0.051	7.443 2.73 0.828 0.189	6.855 2.496 0.492 0.096	6.906 3.9 1.125 0.267	4.939 2.406 1.01 0.344 0.077	2.655 1.031 0.295 0.068	4.779 2.532 1.129 0.369 0.062	1.488 0.894 0.37 0.139 0.026	4.592 2.604 1.107 0.362 0.086	2.454 0.999 0.218 0.05	2.401 1.53 0.533 0.133
2 0.35 3 0.4 4 0.45 5 0.5 6 0.55 Prob. of Select MTD Prob. of Toxicity	0.168 0.091 0.023 0.006 0.002 i3+3 0.615 0.331	0.427 0.225 0.069 0.02 0.001 0 mTPI 0.652 0.327	0.214 0.103 0.021 0.002 0 mTPI-2 0.622 0.328	0.105 0.042 0.008 0.001 0 3+3 0.393 0.332	0.247 0.099 0.028 0.01 0 BOIN 0.694 0.327	0.199 0.068 0.009 0.003 0 BLRM 0.496 0.339	0.258 0.119 0.034 0.003 0 CRM 0.679 0.335	6.717 2.619 0.768 0.168	7.653 2.592 0.657 0.117	7.263 2.898 0.768 0.12	2.469 0.918 0.291 0.051	7.443 2.73 0.828 0.189	6.855 2.496 0.492 0.096	6.906 3.9 1.125 0.267	4.939 2.406 1.01 0.344 0.077	2.655 1.031 0.295 0.068	4.779 2.532 1.129 0.369 0.062	1.488 0.894 0.37 0.139 0.026	4.592 2.604 1.107 0.362 0.086	2.454 0.999 0.218 0.05	2.401 1.53 0.533 0.133
2 0.35 3 0.4 4 0.45 5 0.5 6 0.55 Prob. of Select MTD	0.168 0.091 0.023 0.006 0.002 i3+3 0.615	0.427 0.225 0.069 0.02 0.001 0 mTPI 0.652	0.214 0.103 0.021 0.002 0 mTPI-2 0.622	0.105 0.042 0.008 0.001 0 3+3 0.393	0.247 0.099 0.028 0.01 0 BOIN 0.694	0.199 0.068 0.009 0.003 0 BLRM 0.496	0.258 0.119 0.034 0.003 0 CRM 0.679	6.717 2.619 0.768 0.168	7.653 2.592 0.657 0.117	7.263 2.898 0.768 0.12	2.469 0.918 0.291 0.051	7.443 2.73 0.828 0.189	6.855 2.496 0.492 0.096	6.906 3.9 1.125 0.267	4.939 2.406 1.01 0.344 0.077	2.655 1.031 0.295 0.068	4.779 2.532 1.129 0.369 0.062	1.488 0.894 0.37 0.139 0.026	4.592 2.604 1.107 0.362 0.086	2.454 0.999 0.218 0.05	2.401 1.53 0.533 0.133
2 0.35 3 0.4 4 0.45 5 0.5 6 0.55 Prob. of Select MTD Prob. of Toxicity Prob. of Select Dose-over-MTD	0.168 0.091 0.023 0.006 0.002 i3+3 0.615 0.331 0.122	0.427 0.225 0.069 0.02 0.001 0 mTPI 0.652 0.327 0.09	0.214 0.103 0.021 0.002 0 mTPI-2 0.622 0.328 0.126	0.105 0.042 0.008 0.001 0 3+3 0.393 0.332 0.051	0.247 0.099 0.028 0.01 0 BOIN 0.694 0.327 0.137	0.199 0.068 0.009 0.003 0 BLRM 0.496 0.339 0.08	0.258 0.119 0.034 0.003 0 CRM 0.679 0.335 0.156	6.717 2.619 0.768 0.168	7.653 2.592 0.657 0.117	7.263 2.898 0.768 0.12	2.469 0.918 0.291 0.051	7.443 2.73 0.828 0.189	6.855 2.496 0.492 0.096	6.906 3.9 1.125 0.267	4.939 2.406 1.01 0.344 0.077	2.655 1.031 0.295 0.068	4.779 2.532 1.129 0.369 0.062	1.488 0.894 0.37 0.139 0.026	4.592 2.604 1.107 0.362 0.086	2.454 0.999 0.218 0.05	2.401 1.53 0.533 0.133
2 0.35 3 0.4 4 0.45 5 0.5 6 0.55 Prob. of Select MTD Prob. of Toxicity Prob. of No Selection	0.168 0.091 0.023 0.006 0.002 i3+3 0.615 0.331	0.427 0.225 0.069 0.02 0.001 0 mTPI 0.652 0.327	0.214 0.103 0.021 0.002 0 mTPI-2 0.622 0.328	0.105 0.042 0.008 0.001 0 3+3 0.393 0.332	0.247 0.099 0.028 0.01 0 BOIN 0.694 0.327	0.199 0.068 0.009 0.003 0 BLRM 0.496 0.339	0.258 0.119 0.034 0.003 0 CRM 0.679 0.335	6.717 2.619 0.768 0.168	7.653 2.592 0.657 0.117	7.263 2.898 0.768 0.12	2.469 0.918 0.291 0.051	7.443 2.73 0.828 0.189	6.855 2.496 0.492 0.096	6.906 3.9 1.125 0.267	4.939 2.406 1.01 0.344 0.077	2.655 1.031 0.295 0.068	4.779 2.532 1.129 0.369 0.062	1.488 0.894 0.37 0.139 0.026	4.592 2.604 1.107 0.362 0.086	2.454 0.999 0.218 0.05	2.401 1.53 0.533 0.133
2 0.35 3 0.4 4 0.45 5 0.5 6 0.55 Prob. of Select MTD Prob. of Toxicity Prob. of No Selection Scenario 14	0.168 0.091 0.023 0.006 0.002 i3+3 0.615 0.331 0.122	0.427 0.225 0.069 0.02 0.001 0 mTPI 0.652 0.327 0.09	0.214 0.103 0.021 0.002 0 mTPI-2 0.622 0.328 0.126 0.252	0.105 0.042 0.008 0.001 0 3+3 0.393 0.332 0.051 0.556	0.247 0.099 0.028 0.01 0 BOIN 0.694 0.327 0.137	0.199 0.068 0.009 0.003 0 BLRM 0.496 0.339 0.08	0.258 0.119 0.034 0.003 0 CRM 0.679 0.335 0.156	6.717 2.619 0.768 0.168	7.653 2.592 0.657 0.117	7.263 2.898 0.768 0.12 0.003	2.469 0.918 0.291 0.051 0.003	7.443 2.73 0.828 0.189 0.012	6.855 2.496 0.492 0.096	6.906 3.9 1.125 0.267	4.939 2.406 1.01 0.344 0.077	2.655 1.031 0.295 0.068	4.779 2.532 1.129 0.369 0.062 0.002	1.488 0.894 0.37 0.139 0.026 0.002	4.592 2.604 1.107 0.362 0.086 0.009	2.454 0.999 0.218 0.05	2.401 1.53 0.533 0.133
2 0.35 3 0.4 4 0.45 5 0.5 6 0.55 Prob. of Select MTD Prob. of Toxicity Prob. of Select Dose-over-MTD Prob. of No Selection Scenario 14 Target Toxicity Prob. = 0.3	0.168 0.091 0.023 0.006 0.002 i3+3 0.615 0.331 0.122 0.263	0.427 0.225 0.069 0.02 0.001 0 mTPI 0.652 0.327 0.09 0.258	0.214 0.103 0.021 0.002 0 mTPI-2 0.622 0.328 0.126 0.252	0.105 0.042 0.008 0.001 0 3+3 0.393 0.332 0.051 0.556	0.247 0.099 0.028 0.01 0 BOIN 0.694 0.327 0.137 0.169	0.199 0.068 0.009 0.003 0 BLRM 0.496 0.339 0.08 0.424	0.258 0.119 0.034 0.003 0 CRM 0.679 0.335 0.156 0.165	6.717 2.619 0.768 0.168 0.024	7.653 2.592 0.657 0.117 0	7.263 2.898 0.768 0.12 0.003	2.469 0.918 0.291 0.051 0.003	7.443 2.73 0.828 0.189 0.012	6.855 2.496 0.492 0.096 0.009	6.906 3.9 1.125 0.267 0.015	4.939 2.406 1.01 0.344 0.077 0.011	2.655 1.031 0.295 0.068 0	4.779 2.532 1.129 0.369 0.062 0.002	1.488 0.894 0.37 0.139 0.026 0.002	4.592 2.604 1.107 0.362 0.086 0.009	2.454 0.999 0.218 0.05 0.005	2.401 1.53 0.533 0.133 0.011
2 0.35 3 0.4 4 0.45 5 0.5 6 0.55 Prob. of Select MTD Prob. of Toxicity Prob. of No Selection Scenario 14 Target Toxicity Prob. = 0.3 Dose Level True Tox Prob.	0.168 0.091 0.023 0.006 0.002 i3+3 0.615 0.331 0.122 0.263	0.427 0.225 0.069 0.02 0.001 0 mTPI 0.652 0.327 0.09 0.258	0.214 0.103 0.021 0.002 0 mTPI-2 0.622 0.328 0.126 0.252	0.105 0.042 0.008 0.001 0 3+3 0.393 0.332 0.051 0.556 election Prob	0.247 0.099 0.028 0.01 0 BOIN 0.694 0.327 0.137 0.169	0.199 0.068 0.009 0.003 0 BLRM 0.496 0.339 0.08 0.424	0.258 0.119 0.034 0.003 0 CRM 0.679 0.335 0.156 0.165	6.717 2.619 0.768 0.168 0.024	7.653 2.592 0.657 0.117 0	7.263 2.898 0.768 0.12 0.003	2.469 0.918 0.291 0.051 0.003	7.443 2.73 0.828 0.189 0.012	6.855 2.496 0.492 0.096 0.009	6.906 3.9 1.125 0.267 0.015	4.939 2.406 1.01 0.344 0.077 0.011	2.655 1.031 0.295 0.068 0	4.779 2.532 1.129 0.369 0.062 0.002	1.488 0.894 0.37 0.139 0.026 0.002	4.592 2.604 1.107 0.362 0.086 0.009	2.454 0.999 0.218 0.05 0.005	2.401 1.53 0.533 0.133 0.011
2 0.35 3 0.4 4 0.45 5 0.5 6 0.55 Prob. of Select MTD Prob. of Toxicity Prob. of No Selection Scenario 14 Target Toxicity Prob. = 0.3 Dose Level True Tox Prob. 1 0.15	0.168 0.091 0.023 0.006 0.002 i3+3 0.615 0.331 0.122 0.263	0.427 0.225 0.069 0.02 0.001 0 mTPI 0.652 0.327 0.09 0.258	0.214 0.103 0.021 0.002 0 mTPI-2 0.622 0.328 0.126 0.252 S mTPI-2 0.061	0.105 0.042 0.008 0.001 0 3+3 0.393 0.332 0.051 0.556 election Prob	0.247 0.099 0.028 0.01 0 BOIN 0.694 0.327 0.137 0.169 b. BOIN 0.054	0.199 0.068 0.009 0.003 0 BLRM 0.496 0.339 0.08 0.424	0.258 0.119 0.034 0.003 0 CRM 0.679 0.335 0.156 0.165	6.717 2.619 0.768 0.168 0.024	7.653 2.592 0.657 0.117 0	7.263 2.898 0.768 0.12 0.003 # of mTPI-2 6.801	2.469 0.918 0.291 0.051 0.003 Patients Tro 3+3 4.494	7.443 2.73 0.828 0.189 0.012	6.855 2.496 0.492 0.096 0.009	6.906 3.9 1.125 0.267 0.015	4.939 2.406 1.01 0.344 0.077 0.011	2.655 1.031 0.295 0.068 0	4.779 2.532 1.129 0.369 0.062 0.002 mTPI-2 1.026	1.488 0.894 0.37 0.139 0.026 0.002 # of Toxicities 3+3 0.676	4.592 2.604 1.107 0.362 0.086 0.009	2.454 0.999 0.218 0.05 0.005	2.401 1.53 0.533 0.133 0.011
2 0.35 3 0.4 4 0.45 5 0.5 6 0.55 Prob. of Select MTD Prob. of Toxicity Prob. of Select Dose-over-MTD Prob. of No Selection Scenario 14 Target Toxicity Prob. = 0.3 Dose Level True Tox Prob. 1 0.15 2 0.18	0.168 0.091 0.023 0.006 0.002 i3+3 0.615 0.331 0.122 0.263	0.427 0.225 0.069 0.02 0.001 0 mTPI 0.652 0.327 0.09 0.258	0.214 0.103 0.021 0.002 0 mTPI-2 0.622 0.328 0.126 0.252 SmTPI-2 0.061 0.153	0.105 0.042 0.008 0.001 0 3+3 0.393 0.393 0.392 0.051 0.556 election Prob 3+3 0.212 0.194	0.247 0.099 0.028 0.01 0 BOIN 0.694 0.327 0.137 0.169 b. BOIN 0.054 0.128	0.199 0.068 0.009 0.003 0 BLRM 0.496 0.339 0.08 0.424 BLRM 0.053 0.164	0.258 0.119 0.034 0.003 0 CRM 0.679 0.335 0.156 0.165	6.717 2.619 0.768 0.168 0.024 i3+3 6.633 7.005	7.653 2.592 0.657 0.117 0 mTPI 7.461 7.074	7.263 2.898 0.768 0.12 0.003 # of mTPI-2 6.801 7.029	2.469 0.918 0.291 0.051 0.003 Patients Tro 3+3 4.494 3.741	7.443 2.73 0.828 0.189 0.012 eated BOIN 6.573 7.122	6.855 2.496 0.492 0.096 0.009 BLRM 5.517 7.851	6.906 3.9 1.125 0.267 0.015	4.939 2.406 1.01 0.344 0.077 0.011 i3+3 1.017 1.258	2.655 1.031 0.295 0.068 0	4.779 2.532 1.129 0.369 0.062 0.002 mTPI-2 1.026 1.225	1.488 0.894 0.37 0.139 0.026 0.002 # of Toxicities 3+3 0.676 0.689	4.592 2.604 1.107 0.362 0.086 0.009 BOIN 0.966 1.259	2.454 0.999 0.218 0.05 0.005	2.401 1.53 0.533 0.133 0.011 CRM 0.931 1.022
2 0.35 3 0.4 4 0.45 5 0.5 6 0.55 Prob. of Select MTD Prob. of Toxicity Prob. of No Selection Scenario 14 Target Toxicity Prob. = 0.3 Dose Level True Tox Prob. 1 0.15 2 0.18 3 0.21	0.168 0.091 0.023 0.006 0.002 i3+3 0.615 0.331 0.122 0.263	0.427 0.225 0.069 0.02 0.001 0 mTPI 0.652 0.327 0.09 0.258	0.214 0.103 0.021 0.002 0 mTPI-2 0.622 0.328 0.126 0.252 S mTPI-2 0.061	0.105 0.042 0.008 0.001 0 3+3 0.393 0.332 0.051 0.556 election Prob	0.247 0.099 0.028 0.01 0 BOIN 0.694 0.327 0.137 0.169 b. BOIN 0.054	0.199 0.068 0.009 0.003 0 BLRM 0.496 0.339 0.08 0.424	0.258 0.119 0.034 0.003 0 CRM 0.679 0.335 0.156 0.165	6.717 2.619 0.768 0.168 0.024	7.653 2.592 0.657 0.117 0 mTPI 7.461 7.074 6.774	# of mTPI-2 6.801 7.029 6.36	2.469 0.918 0.291 0.051 0.003 Patients Tro 3+3 4.494	7.443 2.73 0.828 0.189 0.012	6.855 2.496 0.492 0.096 0.009	6.906 3.9 1.125 0.267 0.015	4.939 2.406 1.01 0.344 0.077 0.011	2.655 1.031 0.295 0.068 0	4.779 2.532 1.129 0.369 0.062 0.002 mTPI-2 1.026	1.488 0.894 0.37 0.139 0.026 0.002 # of Toxicities 3+3 0.676	4.592 2.604 1.107 0.362 0.086 0.009	2.454 0.999 0.218 0.05 0.005	2.401 1.53 0.533 0.133 0.011
2 0.35 3 0.4 4 0.45 5 0.5 6 0.55 Prob. of Select MTD Prob. of Toxicity Prob. of No Selection Scenario 14 Target Toxicity Prob. = 0.3 Dose Level True Tox Prob. 1 0.15 2 0.18 3 0.21 4 0.24	0.168 0.091 0.023 0.006 0.002 i3+3 0.615 0.331 0.122 0.263	0.427 0.225 0.069 0.02 0.001 0 mTPI 0.652 0.327 0.09 0.258	0.214 0.103 0.021 0.002 0 mTPI-2 0.622 0.328 0.126 0.252 SmTPI-2 0.061 0.153	0.105 0.042 0.008 0.001 0 3+3 0.393 0.393 0.392 0.051 0.556 election Prob 3+3 0.212 0.194	0.247 0.099 0.028 0.01 0 BOIN 0.694 0.327 0.137 0.169 b. BOIN 0.054 0.228 0.221	0.199 0.068 0.009 0.003 0 BLRM 0.496 0.339 0.08 0.424 BLRM 0.053 0.164	0.258 0.119 0.034 0.003 0 CRM 0.679 0.335 0.156 0.165 CRM 0.041 0.217 0.247	6.717 2.619 0.768 0.168 0.024 i3+3 6.633 7.005	7.653 2.592 0.657 0.117 0 mTPI 7.461 7.074 6.774 4.62	# of mTPI-2 6.801 7.029 6.36 4.833	2.469 0.918 0.291 0.051 0.003 Patients Tra 3+3 4.494 3.741 2.862 1.938	7.443 2.73 0.828 0.189 0.012 eated BOIN 6.573 7.122 6.333 4.923	6.855 2.496 0.492 0.096 0.009 BLRM 5.517 7.851	6.906 3.9 1.125 0.267 0.015	4.939 2.406 1.01 0.344 0.077 0.011 i3+3 1.017 1.258	2.655 1.031 0.295 0.068 0	4.779 2.532 1.129 0.369 0.062 0.002 mTPI-2 1.026 1.225	1.488 0.894 0.37 0.139 0.026 0.002 # of Toxicities 3+3 0.676 0.689 0.606 0.466	4.592 2.604 1.107 0.362 0.086 0.009 BOIN 0.966 1.259	2.454 0.999 0.218 0.05 0.005 0.005	2.401 1.53 0.533 0.133 0.011 CRM 0.931 1.022 1.363 1.323
2 0.35 3 0.4 4 0.45 5 0.5 6 0.55 Prob. of Select MTD Prob. of Toxicity Prob. of No Selection Scenario 14 Target Toxicity Prob. = 0.3 Dose Level True Tox Prob. 1 0.15 2 0.18 3 0.21	0.168 0.091 0.023 0.006 0.002 i3+3 0.615 0.331 0.122 0.263 i3+3 0.057 0.15 0.202	0.427 0.225 0.069 0.02 0.001 0 mTPI 0.652 0.327 0.09 0.258 mTPI 0.082 0.171 0.24	0.214 0.103 0.021 0.002 0 mTPI-2 0.622 0.328 0.126 0.252 SmTPI-2 0.061 0.153 0.207	0.105 0.042 0.008 0.001 0 3+3 0.393 0.332 0.051 0.556 election Prob 3+3 0.212 0.194 0.151	0.247 0.099 0.028 0.01 0 BOIN 0.694 0.327 0.137 0.169 b. BOIN 0.054 0.128 0.208	0.199 0.068 0.009 0.003 0 BLRM 0.496 0.339 0.08 0.424 BLRM 0.053 0.164 0.266	0.258 0.119 0.034 0.003 0 CRM 0.679 0.335 0.156 0.165 CRM 0.041 0.128 0.217	6.717 2.619 0.768 0.168 0.024 i3+3 6.633 7.005 6.387	7.653 2.592 0.657 0.117 0 mTPI 7.461 7.074 6.774	# of mTPI-2 6.801 7.029 6.36	2.469 0.918 0.291 0.051 0.003 Patients Tre 3+3 4.494 3.741 2.862	7.443 2.73 0.828 0.189 0.012 eated BOIN 6.573 7.122 6.333	6.855 2.496 0.492 0.096 0.009 BLRM 5.517 7.851 7.686	6.906 3.9 1.125 0.267 0.015 CRM 6.18 5.841 6.417	4.939 2.406 1.01 0.344 0.077 0.011 i3+3 1.017 1.258 1.353	2.655 1.031 0.295 0.068 0 mTPI 1.115 1.205 1.469	4.779 2.532 1.129 0.369 0.062 0.002 mTPI-2 1.026 1.225 1.357	1.488 0.894 0.37 0.139 0.026 0.002 # of Toxicities 3+3 0.676 0.689 0.606	4.592 2.604 1.107 0.362 0.086 0.009 BOIN 0.966 1.259 1.321	2.454 0.999 0.218 0.05 0.005 0.005	2.401 1.53 0.533 0.133 0.011 CRM 0.931 1.022 1.363
2 0.35 3 0.4 4 0.45 5 0.5 6 0.55 Prob. of Select MTD Prob. of Toxicity Prob. of No Selection Scenario 14 Target Toxicity Prob. = 0.3 Dose Level True Tox Prob. 1 0.15 2 0.18 3 0.21 4 0.24	0.168 0.091 0.023 0.006 0.002 i3+3 0.615 0.331 0.122 0.263 i3+3 0.057 0.15 0.202 0.198	0.427 0.225 0.069 0.02 0.001 0 mTPI 0.652 0.327 0.09 0.258 mTPI 0.082 0.171 0.24 0.24	0.214 0.103 0.021 0.002 0 mTPI-2 0.622 0.328 0.126 0.252 S mTPI-2 0.061 0.153 0.207 0.21	0.105 0.042 0.008 0.001 0 3+3 0.393 0.393 0.332 0.051 0.556 0.212 0.194 0.151 0.111	0.247 0.099 0.028 0.011 0 BOIN 0.694 0.327 0.137 0.169 b. BOIN 0.054 0.128 0.208	0.199 0.068 0.009 0.003 0 BLRM 0.496 0.339 0.08 0.424 BLRM 0.053 0.164 0.266 0.232	0.258 0.119 0.034 0.003 0 CRM 0.679 0.335 0.156 0.165 CRM 0.041 0.128 0.217 0.247	6.717 2.619 0.768 0.168 0.024 i3+3 6.633 7.005 6.387 4.584 2.997	7.653 2.592 0.657 0.117 0 mTPI 7.461 7.074 6.774 4.62 2.334	# of mTPI-2 6.801 7.029 6.36 4.833 2.934	2.469 0.918 0.291 0.051 0.003 Patients Tro 3+3 4.494 3.741 2.862 1.938	7.443 2.73 0.828 0.189 0.012 eated BOIN 6.573 7.122 6.333 4.923	6.855 2.496 0.492 0.096 0.009 BLRM 5.517 7.851 7.686 4.377 1.962	CRM 6.18 5.841 6.417 5.484 3.657	4,939 2,406 1.01 0.344 0.077 0.011 i3+3 1.017 1.258 1.353 1.061	2.655 1.031 0.295 0.068 0 mTPI 1.115 1.205 1.469	4.779 2.532 1.129 0.369 0.062 0.002 mTPI-2 1.026 1.225 1.357 1.168 0.771	1.488 0.894 0.37 0.139 0.026 0.002 # of Toxicities 3+3 0.676 0.689 0.606 0.466 0.338	4.592 2.604 1.107 0.362 0.086 0.009 8 BOIN 0.966 1.259 1.321 1.169 0.789	2.454 0.999 0.218 0.05 0.005 0.005	2.401 1.53 0.533 0.133 0.011 CRM 0.931 1.022 1.363 1.323 0.981
2 0.35 3 0.4 4 0.45 5 0.5 6 0.55 Prob. of Select MTD Prob. of Toxicity Prob. of Select Dose-over-MTD Prob. of No Selection Scenario 14 Target Toxicity Prob. = 0.3 Dose Level True Tox Prob. 1 0.15 2 0.18 3 0.21 4 0.24 5 0.27	0.168 0.091 0.023 0.006 0.002 i3+3 0.615 0.331 0.122 0.263 i3+3 0.057 0.15 0.202 0.198 0.192	0.427 0.225 0.069 0.02 0.001 0 mTPI 0.652 0.327 0.09 0.258 mTPI 0.082 0.171 0.24 0.227 0.137 0.134	0.214 0.103 0.021 0.002 0 mTPI-2 0.622 0.328 0.126 0.252 SmTPI-2 0.061 0.153 0.207 0.21 0.18	0.105 0.042 0.008 0.001 0 3+3 0.393 0.393 0.351 0.556 election Prot 3+3 0.212 0.194 0.151 0.111	0.247 0.099 0.028 0.01 0 BOIN 0.694 0.327 0.137 0.169 b. BOIN 0.054 0.128 0.208 0.21 0.183 0.198	0.199 0.068 0.009 0.003 0 BLRM 0.496 0.339 0.08 0.424 BLRM 0.053 0.164 0.266 0.232 0.118 0.114	0.258 0.119 0.034 0.003 0 CRM 0.679 0.335 0.156 0.165 CRM 0.041 0.128 0.217 0.247 0.204 0.155	6.717 2.619 0.768 0.168 0.024 i3+3 6.633 7.005 6.387 4.584	7.653 2.592 0.657 0.117 0 mTPI 7.461 7.074 6.774 4.62	# of mTPI-2 6.801 7.029 6.36 4.833	2.469 0.918 0.291 0.051 0.003 Patients Tra 3+3 4.494 3.741 2.862 1.938	7.443 2.73 0.828 0.189 0.012 eated BOIN 6.573 7.122 6.333 4.923 2.952	6.855 2.496 0.492 0.096 0.009 BLRM 5.517 7.851 7.686 4.377	6.906 3.9 1.125 0.267 0.015 CRM 6.18 5.841 6.417 5.484	4,939 2,406 1,01 0,344 0,077 0,011 i3+3 1,017 1,258 1,353 1,061	2.655 1.031 0.295 0.068 0 0 mTPI 1.115 1.205 1.469 1.105	4.779 2.532 1.129 0.369 0.062 0.002 mTPI-2 1.026 1.225 1.357 1.168	1.488 0.894 0.37 0.139 0.026 0.002 # of Toxicities 3+3 0.676 0.689 0.606 0.466	4.592 2.604 1.107 0.362 0.086 0.009	2.454 0.999 0.218 0.05 0.005 0.005	2.401 1.53 0.533 0.133 0.011 CRM 0.931 1.022 1.363 1.323
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2 0.35 3 0.4 4 0.45 5 0.5 6 0.55 Prob. of Select MTD Prob. of Select Dose-over-MTD Prob. of No Selection Scenario 14 Target Toxicity Prob. = 0.3 Dose Level True Tox Prob. 1 0.15 2 0.18 3 0.21 4 0.24 5 0.27 6 0.3 Prob. of Select MTD Prob. of Select MTD	0.168 0.091 0.023 0.006 0.002 i3+3 0.615 0.331 0.122 0.263 i3+3 0.057 0.15 0.202 0.198 0.192 0.181 i3+3 0.373 0.205	0.427 0.225 0.069 0.02 0.001 0 mTPI 0.652 0.327 0.09 0.258 mTPI 0.082 0.171 0.24 0.227 0.137 0.134 mTPI 0.211 0.199	0.214 0.103 0.021 0.002 0 mTPI-2 0.622 0.328 0.126 0.252 SmTPI-2 0.061 0.153 0.207 0.21 0.18 mTPI-2 0.36 0.204	0.105 0.042 0.008 0.001 0 3+3 0.393 0.352 0.0556 election Prot 3+3 0.212 0.191 0.151 0.111 0.069 3+3 0.129 0.066 3+3 0.199	0.247 0.099 0.028 0.01 0 BOIN 0.694 0.327 0.137 0.169 b. BOIN 0.054 0.128 0.208 0.221 0.183 0.198 BOIN 0.304	0.199 0.068 0.009 0.003 0 BLRM 0.496 0.339 0.08 0.424 BLRM 0.053 0.164 0.266 0.232 0.118 0.114 BLRM 0.232 0.119	0.258 0.119 0.034 0.003 0 CRM 0.679 0.335 0.156 0.165 CRM 0.041 0.128 0.217 0.247 0.204 0.155 CRM 0.359 0.21	6.717 2.619 0.768 0.168 0.024 i3+3 6.633 7.005 6.387 4.584 2.997	7.653 2.592 0.657 0.117 0 mTPI 7.461 7.074 6.774 4.62 2.334	# of mTPI-2 6.801 7.029 6.36 4.833 2.934	2.469 0.918 0.291 0.051 0.003 Patients Tro 3+3 4.494 3.741 2.862 1.938	7.443 2.73 0.828 0.189 0.012 eated BOIN 6.573 7.122 6.333 4.923 2.952	6.855 2.496 0.492 0.096 0.009 BLRM 5.517 7.851 7.686 4.377 1.962	CRM 6.18 5.841 6.417 5.484 3.657	4,939 2,406 1,01 0,344 0,077 0,011 i3+3 1,017 1,258 1,353 1,061	2.655 1.031 0.295 0.068 0 0 mTPI 1.115 1.205 1.469 1.105	4.779 2.532 1.129 0.369 0.062 0.002 mTPI-2 1.026 1.225 1.357 1.168 0.771	1.488 0.894 0.37 0.139 0.026 0.002 # of Toxicities 3+3 0.676 0.689 0.606 0.466 0.338	4.592 2.604 1.107 0.362 0.086 0.009 8 BOIN 0.966 1.259 1.321 1.169 0.789	2.454 0.999 0.218 0.05 0.005 0.005	2.401 1.53 0.533 0.133 0.011 CRM 0.931 1.022 1.363 1.323 0.981

Appendix D Comparison of decision tables for different designs

We provide a quick comparison of decision tables among the i3+3, mTPI, and mTPI-2 designs, since all three designs require the same input of the target toxicity probability p_T and the EI. Figure A1 provides a side-by-side comparison based on $p_T=0.3$ and EI [0.25, 0.35] for up to 9 patients. The dose assignment decisions for i3+3 seems to be more reasonable than mTPI or mTPI-2. For example, when 1 out of 2 patients experiences DLT, the decision is "S" under i3+3 and mTPI, compared with the decision "D" under mTPI-2. Here, one could argue that when only 2 patients have been treated at a dose, 1 DLT does not provide sufficient information to warrant a de-escalation decision. Investigators might want to wait for further information to make a dose change decision. In this case, i3+3 agrees with mTPI, not mTPI-2. As a contrasting example, when 3 out of 6 patients experiences DLTs, the decision is "D" under i3+3 and mTPI-2, compared with the decision "S" under mTPI. Again, one could argue that "S" is more sensible according to our earlier discussion. Therefore, i3+3 here agrees with mTPI-2, not mTPI. In general, we can see that i3+3 seems to take more sound and ethically acceptable decisions, often complementing the mTPI and mTPI-2 designs.

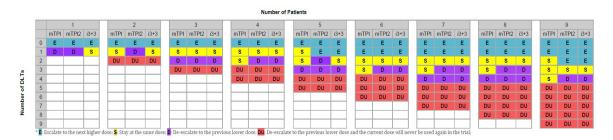
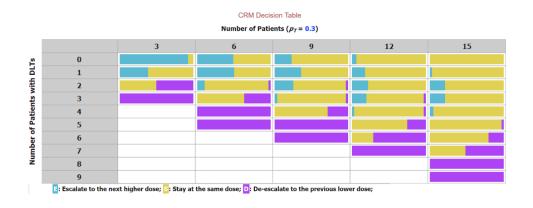


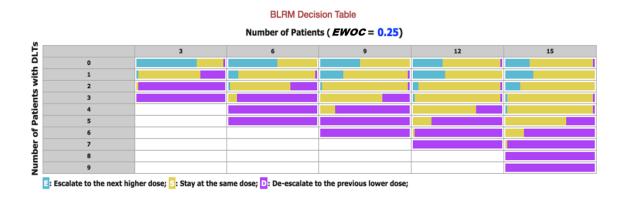
Figure A1: Comparison of the decision tables for i3+3, mTPI and mTPI-2. For each "Number of Patients" (column), there are three subcolumns listing the decisions of i3+3, mTPI, and mTPI-2 side-by-side corresponding to the "Number of DLTs" (row). Here, the target toxicity probability $p_T = 0.3$ and EI (0.25, 0.35).

Other than the slightly different decision tables, all three designs use the same statistical models and inference to select the MTD. As the mTPI and mTPI-2 designs have been well established in the literature with desirable performance (Ji et al., 2010; Guo et al., 2017; Ji and Yang, 2018; Zhou et al, 2018), we decide not to conduct more and larger simulations. The i3+3 design is expected to perform at a similar level as the mTPI and mTPI-2 designs due to its similar but slightly improved decision table, which puts i3+3 in par with other major model-based designs.

While the decisions of the i3+3 design can be calculated and tabulated prior to the trial onset, the decisions of the model-based design such as CRM and BLRM require intensive computation and simulation to investigate. In particular, for each row and column in Figure A2, while the decision of i3+3 is fixed, that of CRM and BLRM is random and takes "D", "S", or "E" following a probability

distribution. See Ji and Yang (2018) for a detailed discussion. To investigate the behavior of the CRM and BLRM designs, we summarize the empirical distribution of the random decisions by computing the frequencies of "D", "S", "E" for each column and row value given the observed toxicity data corresponding to the row and column numbers. The frequencies of the three decisions are plotted in terms of horizontal color bars shown in Figure A2, with the bar length proportional to the frequency.





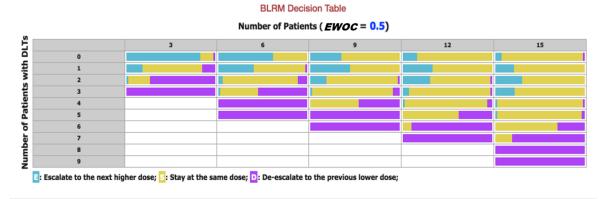


Figure A2: Decision tables under the CRM and BLRM design for $p_T = 0.3$. Each column represents n number of patients treated at the current dose and each row represents x number of patients with DLTs. For each entry, the decisions E, S, and D are colored blue, yellow, and purple, respectively. The length of the colored segments within each bar are proportional to the three proportions of the three decisions taken by CRM and BLRM for a given (x; n) data point from a simulation study using the 14 scenarios in Appendix B and 10,000 simulated trials per scenarios.

It can be seen from the table that more than half of the times the CRM design would stay, and about

one fifth of the times the BLRM (with EWOC=0.5) design would de-escalate when 1 out of 3 patients experienced DLT at a given dose. When 3 out of 6 patients experienced DLT, about half of the times CRM and BLRM (with EWOC=0.5) would de-escalate but the other half of the times it would stay. These decisions may not pass safety review committees in real-world clinical trialsn real-world clinical trials.