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Isotonic Design for Phase I Clinical Trials: Can We Improve Further?

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Abstract

One of the most challenging tasks in clinical trials is finding the maximum tolerated dose (MTD) to be tested in the next phase. An assurance for the safety of the patients and recommendation of a suitable dose for phase II are the main objectives of a phase I trial. The MTD can be identified through various approaches. A non-parametric approach, known as the isotonic design, has been explored in our study. The design relies on the monotonicity assumption of the dose-toxicity relationship. Usually the number of patients in a trial have an impact on the adequacy of dose recommendation. This paper is a humble attempt to see the impact of cohort size and total cohorts on the isotonic design. It investigates the possibility of improving the current algorithm of the isotonic design for escalation and de-escalation. Also, the paper proposes a stopping rule to avoid any severely toxic dose as the MTD. The simulation study shows that along with total cohort, cohort size also has an appreciable effect on the MTD selection. The proposed modification of the algorithm has also been found to work satisfactorily in majority of the cases.

Keywords: Phase I trial, dose-finding studies, maximum tolerated dose, isotonic design, stopping rule.

1. Introduction

Clinical trials play a vital role in the survival of mankind by discovering new treatments for diseases, as well as new ways to detect, diagnose and reduce the risk of diseases. When a new drug or treatment is found promising in preclinical stage, researchers want to test it in humans though clinical trials. Clinical trials are conducted in four phases, each having specific objectives. The main reason for doing phase I studies is to find the highest dose of the new drug that can be given safely without causing serious side effects. It is usually tested in a small cohort or group of patients or volunteers of size 20-80 for the first time.

There are a number of rule-based and model-based designs for dose finding in phase I clinical trials. Leung and Wang (2001) introduced a model-free approach which is easy to conduct and free from parametric assumption. This design performs better than the most commonly used methods, and it compares favorably with other phase I designs. The authors also said that their proposed method can be easily changed to optimise efficiency based on each trial's requirement. For example, one may consider starting at another dose level rather than the

lowest dose level or by using a different cohort size. Since isotonic design is a non-parametric approach, it is easy to implement.

Stylianou and Flournoy (2002) tried to find a dose that had a pre-specified toxicity rate in the target population. They used the up-and-down biased coin design introduced by Durham and Flournoy (1994) and investigated five estimators of the target dose, which are derived using maximum likelihood, weighted least squares, sample averages and isotonic regression. They found that a linearly interpolated isotonic regression estimate is simple to derive and performs as well as or better than other target dose estimators in terms of mean square error and the average number of subjects needed for convergence in most of the scenarios studied.

Yuan and Chappell (2004) extended up-and-down design, isotonic design and the continual reassessment method to multiple risk groups with two-way isotonic regression. The only assumption about the groups is that they can be ordered according to their toxicity risk. The first two extensions, in particular, are non-parametric and are easy for clinicians to understand. They worked with different scenarios and found that the escalation rules of multiple risk groups can be linked requiring no parametric assumption about the group toxicity curve and to ensure non-conflicting dosage recommendations.

Ivanova and Flournoy (2009) compared several designs based on the isotonic estimation of dose-toxicity curve in trials with binary outcomes. They concluded that the decision rule in which the next assignment is the dose having probability of toxicity closest to the target, does not work well for the non-parametric designs. They developed a cumulative cohort design in which the next dose depends on the distance between the estimated toxicity rate at the current dose and the target quantile. The utility of isotonic regression for dose finding in phase I trials has been widely discussed in Rosenberger and Haines (2002), Potter (2006), Neuenschwander, Branson, and Gsponer (2008), Le Tourneau, Lee, and Siu (2009), Ivanova and Kim (2009), Oron and Hoff (2013) and Liu and Yuan (2015),

In this paper, we investigate whether the efficiency of the design increases for the increased cohort size and the total number of cohorts in a trial. Also, we present a modified algorithm for the isotonic design to accelerate the dose-escalation. A stopping rule is aimed so that no dose is recommended as the MTD when all the available doses are too toxic. The paper is organized as follows. In Section 2, we summarize the algorithms and stopping rules for the designs. The simulation settings are detailed in Section 3. Section 4 includes the numerical findings of the study. Finally, Section 5 appears with the discussion.

2. Methodology

The section begins with the isotonic design available in the literature. It is followed by our proposal for modification of the isotonic design. Also, here we introduce a simple stopping rule to avoid any unnecessary doses to appear as the MTD.

2.1. Isotonic design

The isotonic design (Leung and Wang 2001) is a model-free approach and it assumes that toxicity is non-decreasing with dose. The traditional 3+3 design summarises toxicity risk at a dose by using the data observed at that dose, which indicates that the design violates monotonicity assumption. However, the isotonic design considers the non-decreasing nature of toxicity.

For an experimental drug, assume that we have k doses with non-decreasing toxicity probabilities. Starting with the lowest dose, cohorts of patients are treated sequentially until a dose is recommended as the MTD. When the monotonicity assumption is violated, we use a pooled estimate of toxicity to maintain the monotonicity. That is, if k dose levels have been tested, the risk of toxicity at dose d_i $(1 \leqslant i \leqslant k)$ must satisfy the monotonicity relationship. For any dose d_r below d_i $(r \leqslant i)$ and any dose d_s above d_i $(s \geqslant i)$, the pooled estimate of risk

can be expressed as

$$w_{r,i,s} = \frac{\sum_{j=r}^{s} \text{Number of toxicities at } d_j}{\sum_{j=r}^{s} \text{Number tested at } d_j}. \tag{1}$$

The risk q_i at dose d_i can be estimated using the isotonic regression

$$\hat{q}_i = \min_{i \leqslant s \leqslant k} \max_{1 \leqslant r \leqslant i} w_{r,i,s}. \tag{2}$$

The $\hat{q}_i$ must be at least as large as any of $w_{1,i,s}$, $w_{2,i,s}$, ..., $w_{i,i,s}$ (or the maximum of these) for any s ($s \geqslant i$). Similarly, $\hat{q}_i$ must be smaller than any of $w_{r,i,i}$, $w_{r,i,i+1}$, ..., $w_{r,i,k}$ (or the minimum of these) for any r ($r \leqslant i$).

Starting with the lowest dose d_1, the algorithm of method can be summarised as follows:

1. Treat a cohort of c patients at d_i. The initial cohort gets d_1.
2. Obtain the pooled estimate of toxicity at different doses using (2), and select that dose at which $\hat{q}_i$ is closest to the target toxicity rate γ, where i is the dose level last used.

   If $\hat{q}_i < \gamma$, then

   $$\begin{cases} \text{escalate if } \gamma - \hat{q}_i \geq \hat{q}_{i+1} - \gamma, & i < k \\ \text{continue at the same dose,} & \text{otherwise.} \end{cases}$$

   If $\hat{q}_i \geqslant \gamma$, then

   $$\begin{cases} \text{de-escalate if } \gamma - \hat{q}_{i-1} < \hat{q}_i - \gamma, & i > 1 \\ \text{continue at the same dose,} & \text{otherwise.} \end{cases}$$

3. Continue steps 1-2 until the stopping rule is met.

Unlike many rule-based designs, this design has the flexibility to choose any percentile as the target rate of toxicity. In this design, usually more than six patients are treated at the MTD, which lessens the variability in the estimate of the MTD.

2.2. Modified isotonic design

Here we propose a modification of the isotonic design to accelerate dose escalation. The algorithm of the proposed design is defined in a way so that it moves faster to the upward direction and slower to the downward direction. More specifically, we change step (2) in the original algorithm in the following way.

If $\hat{q}_i < \gamma$, then

$$\begin{cases} \text{escalate if } \gamma - \hat{q}_i \geq w_1(\hat{q}_{i+1} - \gamma), & \text{i <k} \\ \text{continue at the same dose,} & \text{otherwise.} \end{cases}$$

If $\hat{q}_i \geqslant \gamma$, then

$$\begin{cases} \text{de-escalate if } \gamma - \hat{q}_{i-1} < w_2(\hat{q}_i - \gamma), & i > 1 \\ \text{continue at the same dose,} & \text{otherwise.} \end{cases}$$

In particular, we use $w_1 = 2/3$ and $w_2 = 2$. The main idea is to make the dose escalation faster decreasing the quantity $q_{i+1} - \gamma$. Since this difference gets smaller because of w_1, escalation is relatively easier compared to that at the original algorithm. On the other hand, the choice of w_2 restricts de-escalation by increasing the quantity $\hat{q}_i - \gamma$. Compared to the original version, now it is harder for $\gamma - \hat{q}_{i-1}$ to be smaller than the quantity in the right hand side more often. Similarly, we can choose some other weights if we want to fast/slow escalation or de-escalation in a trial.

2.3. Stopping rules

In the original paper, a trial is stopped based on two criteria: if the same dose has been assigned consecutively to 3 or 4 cohorts or if the trial reaches a sample of 24 patients. The MTD is defined as the dose indicated for the next cohort when the trial stops. However, in our simulation study, we stop a trial only when it reaches the total number of cohorts n.

We also propose a new stopping rule to be used with the isotonic design. This is motivated by the fact that in a situation where none of the available doses has the probability of toxicity below the target toxicity rate, a design should not recommend any dose as the MTD. The stopping rule that comes with the original design fails to handle this issue. The proposed stopping rule is conceptually simple. If $\hat{q}_{i+1} - \gamma > 0.07$ and $n - m \leq 1$, then a trial is stopped with no dose recommended as the MTD. Here $\hat{q}_{i+1}$ is the estimated probability of toxicity at the dose selected for the next cohort and m is the frequency of the dose that has been applied most of the times to the cohorts in a trial. Getting $n - m \leq 1$ at the end of a trial means that almost all the cohorts in the trial has recieved the same dose. The main idea of such stopping rule is that if the same dose is repeated mostly in a trial and also the estimated toxicity at the recommended dose is higher than the target toxicity rate, it would not be ethically appropriate to recommend an MTD. If the proposed condition is not met in a trial, it then recommends an MTD as the dose that would be allocated to the next cohort if that were in the trial.

2.4. Bayesian optimal interval design

Liu and Yuan (2015) proposed the Bayesian optimal interval (BOIN) design to determine the MTD and also to minimize the probability of inappropriate dose assignments to the patients. Assume that n_i patients have been treated at dose level i and l_i be the number of patients who have experienced toxicity at this dose. Let $\hat{p}_i = l_i/n_i$ be the probability of observed toxicity at dose level i. The design assumes prespecified boundaries λ_1 and λ_2 such that $0 \leq \lambda_1 < \lambda_2 \leq 1$. The values of λ_1 and λ_2 can be found for a choice of target toxicity rate, as indicated by the authors. They showed that values of λ_1 and λ_2 increases as target toxicity rate increases. Starting with the lowest dose applied to a cohort of patients, the design escalates to the next dose if $\hat{p}_i \leq \lambda_1$. If $\hat{p}_i \geq \lambda_2$, it de-escalates to the previous dose level. In the other cases, that is, if $\lambda_1 < \hat{p}_i < \lambda_2$, the design suggests staying at the same dose level. The trial is continued until the maximum sample size is exahusted. The design also allows the trial to stop early because of excessive toxicity. More specifically, if $\Pr(p_i > \gamma | l_i, n_i) > 0.95$ and $n_i \geq 3$, dose levels i and higher are eliminated from the trial, and the trial is terminated if the first dose level is eliminated. Given that the trial has not stopped early for toxicity, that dose is selected as the MTD for which the isotonic estimate of probability of toxicity is closest to the target toxicity rate γ.

3. Simulation set up

Nine different dose-response scenarios, taken from Leung and Wang (2001), are considered in our simulation study. Let q_i represent the true probability of toxicity at dose level i, where $i = \{1, \ldots, 6\}$. Some scenarios have slow increase in toxicity, while others have sharp increase. The last scenario is different from the rest eight scenarios in a way that the toxicity probabilities at various dose levels are all higher than the target toxicity rate, $\gamma = 0.33$. Upon receiving a dose by a cohort, the outcomes are generated from a binomial distribution using the corresponding toxicity probability in a scenario.

Each trial starts with the lowest dose applied to the first cohort. After obtaining outcomes for the first cohort, an appropriate dose is chosen by the design criterion for the next cohort, and the procedure continues until meeting the stopping rules. We investigate the design for varying n, such as 24, 36 and 48. As indicated earlier, the dose that would be allocated

to cohort $n+1$, if that were in the trial, is regarded as the MTD. Each of the scenarios is investigated through 5000 simulated trials using a self-written code in `R`.

To compare the isotonic and modified-isotonic designs, we also produce results for the BOIN design. The same simulation set up is followed for this to make the results comparable with isotonic designs. Since the target toxicity rate is 0.33, we obtain the boundaries as $\lambda_1 = 0.260$ and $\lambda_2 = 0.395$. The `R` package `BOIN` is used to obtain the results.

4. Numerical findings

The percentage distribution of MTD selection and dose allocation obtained for different scenarios due to various choices of cohort size (c) and total cohorts (n) are shown in Table 1. These numerical results are produced using the original isotonic design. Different cohorts of size 3 and 6 have been explored. The total number of cohorts that have been explored against the cohort size 3 are 8, 12 and 16. However, these are 4, 6 and 8 against the cohort size 6. The combination has been chosen in a way so that the total number of patients that get engaged are 24, 36 and 48. For a given cohort of size 3 or 6, if we increase the total number of cohorts, the identification of the true MTD improves for the scenarios. For instance, when 8 cohorts of each size 3 are used, then 40.2% times the true MTD gets selected in Scenario 1. If we double the total cohorts, the correct identification increases to 47.6%. If each cohort is of size 6 and the total cohorts is 4, 44.0% of the trials can correctly identify the MTD for this scenario.

Given that the same number of patients are used, the design with larger cohort size (6) is able to identify the MTD more accurately. This is reflected in almost all the scenarios. In Scenario 4, when the total cohorts is 4, 88.4% times dose 5 is selected as the MTD, whereas when the total cohorts is 6, 50.3% times dose 5 is recommended as the MTD. Since the design does not skip any dose during escalation, and four cohorts are involved in a trial, the final dose recommended is the fifth dose, which is coincidently the true MTD. When total cohorts is 6, the dose beyond the fifth one is selected often. So the figure 88.4% appears, as the design is halted due to the availability of four cohorts only in a trial. Similar explanation is appropriate when the total cohorts is 4 in Scenario 8. It has been found that when the true MTD lies towards the upper end of a dose region, the increase in the number of patients ensures improvement in the correct identification of the MTD. However, the improvement is little if the true MTD lies towards the beginning of a dose region.

Table 2 presents the results obtained for the modified isotonic design proposed in Section 2.2. Appreciable reduction of the toxic doses as the MTD has been found for the scenarios. In Scenario 1, while the original version of the design identifies 19.0% times dose level 5 as the MTD, the modified version identifies it 13.8% times. The modified version also allocates less number of patients to the toxic doses during a trial. In Scenario 3, the new version identifies 68.5% times dose level 1 as the MTD, compared to 58.2% times by the old algorithm. Also, in Scenario 7, when the cohort size is 4 and the total cohorts is 8, the proposed algorithm identifies 88.4% times the first two doses as the MTD, while the old approach identifies them in 82.5% of the trials. Performance of the modified isotonic design is also better in Scenario 3 than its counterpart. There is also an improvement in the results for Scenario 4. Results for the modified design are slightly disappointing in Scenarios 6 and 8. In Scenario 6, dose level 2 has very low probability of toxicity compared to that at level 3. Therefore, if we apply the modified algorithm in this scenario, it will slow down the dose escalation towards highly toxic doses. As we have slowed down the process, more trials have appeared with dose 1 as the MTD than the original version. So it has increased the percentage of dose level 1 to be recommended as the MTD. It would be worth mentioning that in the modified version, the percentages of MTD selection and dose allocation for "Below MTD" have increased compared to those for the original algorithm. However, these percentages have decreased appreciably for "Above MTD" in the modified isotonic design.

Table 1: The percentage distribution of MTD and dose allocation (in parenthesis) obtained for various choices of cohort size and total cohorts when the original isotonic design is used. The bold values indicate the recommendation of the true MTD. Note that c and n denote the cohort size and total cohorts, respectively.

Sce.	c	n	Dose Level						Below MTD	Above MTD
			1	2	3	4	5	6		
			q_1(0.05)	q_2(0.10)	q_3(0.20)	q_4(0.30)	q_5(0.50)	q_6 (0.70)		
		8	2.9(16.7)	10.8(22.9)	23.6(27.6)	**40.2**(23.3)	19.0(8.5)	3.6(0.9)	37.3(67.2)	22.6(9.4)
	3	12	3.0(12.2)	10.4(18.7)	23.6(26.5)	**45.3**(29.6)	16.5(11.7)	1.2(1.3)	37.0(57.4)	17.7(13.0)
1		16	2.9(9.9)	10.2(16.6)	24.1(26.2)	**47.6**(33.4)	14.8(12.8)	0.5(1.2)	37.2(52.7)	15.3(14.0)
		4	0.2(26.1)	4.1(29.2)	27.1(30.5)	**44.0**(14.3)	24.6(0.0)	0.0(0.0)	31.4(85.8)	24.6(0.0)
	6	6	0.2(17.5)	2.7(20.7)	22.3(28.7)	**47.5**(24.0)	23.9(8.4)	3.5(0.7)	25.2(66.9)	27.4(9.1)
		8	0.0(13.1)	2.2(16.2)	21.1(27.3)	**55.8**(30.4)	19.2(11.8)	1.6(1.2)	25.3(46.6)	20.8(13.0)
			q_1(0.09)	q_2(0.16)	q_3(0.27)	q_4(0.38)	q_5(0.57)	q_6 (0.75)		
		8	6.5(21.6)	20.0(29.3)	**34.7**(29.3)	29.5(16.1)	8.3(3.6)	1.0(0.3)	26.5(50.9)	38.8(20.0)
	3	12	7.5(15.1)	19.1(24.4)	**36.0**(32.1)	32.8(22.9)	4.2(4.9)	0.3(0.4)	26.6(39.5)	37.3(28.2)
2		16	1.6(28.8)	15.3(34.4)	**40.3**(28.2)	32.5(8.6)	10.3(0.0)	0.0(0.0)	16.9(63.2)	42.8(8.6)
		4	1.7(28.9)	15.3(34.6)	**40.7**(28.3)	31.8(8.2)	10.5(0.0)	0.0(0.0)	17.0(63.5)	42.3(8.2)
	6	6	1.1(19.3)	12.4(27.8)	**40.6**(32.5)	35.3(16.6)	9.7(3.5)	1.0(0.2)	13.5(47.1)	46.0(20.3)
		8	1.2(15.3)	11.9(24.2)	**42.0**(34.1)	37.6(21.5)	6.9(4.7)	0.4(0.3)	13.1(39.5)	44.9(26.5)
			q_1(0.30)	q_2(0.40)	q_3(0.52)	q_4(0.61)	q_5(0.76)	q_6 (0.87)		
		8	**58.2**(64.9)	32.4(27.7)	8.3(6.6)	1.0(0.7)	0.1(0.0)	0.0(0.0)	0.0(0.0)	41.8(35.0)
	3	12	**58.5**(62.8)	33.8(29.1)	7.1(7.3)	0.6(0.8)	0.0(0.0)	0.0(0.0)	0.0(0.0)	41.5(37.5)
3		16	**60.2**(62.2)	32.9(29.8)	6.5(7.3)	0.4(0.7)	0.0(0.0)	0.0(0.0)	0.0(0.0)	39.8(37.8)
		4	**57.3**(68.4)	32.9(26.5)	8.8(5.0)	1.0(0.2)	0.0(0.0)	0.0(0.0)	0.0(0.0)	42.7(31.7)
	6	6	**59.2**(65.4)	33.8(28.3)	6.2(5.8)	0.7(0.5)	0.0(0.0)	0.0(0.0)	0.0(0.0)	40.8(34.6)
		8	**59.8**(63.9)	34.7(29.6)	5.1(6.0)	0.3(0.5)	0.0(0.0)	0.0(0.0)	0.0(0.0)	40.2(36.1)
			q_1(0.00)	q_2(0.00)	q_3(0.04)	q_4(0.09)	q_5(0.25)	q_6 (0.49)		
		8	0.0(12.5)	0.3(12.7)	2.2(15.1)	16.8(21.1)	**47.3**(25.9)	33.3(12.7)	19.3(61.4)	33.3(12.7)
	3	12	0.0(8.3)	0.3(8.5)	2.3(10.9)	15.7(19.3)	**54.1**(34.4)	27.6(18.6)	18.3(47.0)	27.6(18.6)
4		16	0.0(6.2)	0.5(6.6)	2.4(8.8)	16.3(18.8)	**57.0**(39.3)	23.9(20.2)	19.2(40.4)	23.9(20.2)
		4	0.0(25.0)	0.0(25.0)	0.4(25.6)	11.2(24.4)	**88.4**(0.0)	0.0(0.0)	11.6(100.0)	0.0(0.0)
	6	6	0.0(16.7)	0.0(16.7)	0.1(17.1)	7.5(19.7)	**50.3**(22.0)	42.1(7.9)	7.6(70.1)	42.1(7.9)
		8	0.0(12.5)	0.0(12.5)	0.1(12.9)	5.3(16.5)	**61.5**(29.7)	33.2(16.0)	5.4(54.4)	33.2(16.0)
			q_1(0.20)	q_2(0.90)	q_3(0.90)	q_4(0.90)	q_5(0.90)	q_6 (0.90)		
		8	**98.6**(87.8)	1.4(12.2)	0.0(0.0)	0.0(0.0)	0.0(0.0)	0.0(0.0)	0.0(0)	1.4(12.2)
	3	12	**99.6**(91.5)	0.4(8.5)	0.0(0.0)	0.0(0.0)	0.0(0.0)	0.0(0.0)	0.0(0)	0.4(8.5)
5		16	**99.7**(93.6)	0.3(6.4)	0.0(0.0)	0.0(0.0)	0.0(0.0)	0.0(0.0)	0.0(0.0)	0.3(6.4)
		4	**96.3**(76.9)	3.7(23.1)	0.0(0.0)	0.0(0.0)	0.0(0.0)	0.0(0.0)	0.0(0.0)	3.7(23.1)
	6	6	**98.8**(83.7)	1.2(16.3)	0.0(0.0)	0.0(0.0)	0.0(0.0)	0.0(0.0)	0.0(0.0)	1.2(16.3)
		8	**99.5**(87.5)	0.5(12.5)	0.0(0.0)	0.0(0.0)	0.0(0.0)	0.0(0.0)	0.0(0.0)	0.5(12.6)
			q_1(0.10)	q_2(0.20)	q_3(0.90)	q_4(0.90)	q_5(0.90)	q_6 (0.90)		
		8	11.3(25.6)	**87.3**(63.4)	1.5(11.0)	0.0(0.0)	0.0(0.0)	0.0(0.0)	11.3(25.6)	1.5(11.0)
	3	12	11.1(20.8)	**88.6**(71.6)	0.3(7.6)	0.0(0.0)	0.0(0.0)	0.0(0.0)	11.1(20.8)	0.3(7.6)
6		16	10.9(18.4)	**89.0**(75.9)	0.1(5.7)	0.0(0.0)	0.0(0.0)	0.0(0.0)	10.9(18.4)	0.1(5.7)
		4	3.7(30.6)	**87.9**(49.3)	8.5(20.1)	0.0(0.0)	0.0(0.0)	0.0(0.0)	3.7(30.6)	8.5(20.1)
	6	6	2.6(21.2)	**95.4**(63.3)	2.0(15.4)	0.0(0.0)	0.0(0.0)	0.0(0.0)	2.6(21.2)	2.0(15.4)
		8	2.2(16.7)	**97.0**(71.3)	0.8(12.0)	0.0(0.0)	0.0(0.0)	0.0(0.0)	2.2(16.7)	0.8(12.0)
			q_1(0.30)	q_2(0.30)	q_3(0.50)	q_4(0.50)	q_5(0.50)	q_6 (0.50)		
		8	**44.7**(58.7)	**37.8**(28.5)	13.7(10.9)	2.7(1.6)	0.8(0.2)	0.3(0.0)	0.0(0.0)	17.5(12.7)
	3	12	**42.0**(52.8)	**43.4**(33.2)	12.0(11.8)	2.0(1.8)	0.4(0.3)	0.2(0.1)	0.0(0.0)	14.6(14.0)
7		16	**40.8**(50.3)	**45.1**(35.5)	11.5(11.8)	2.0(2.0)	0.4(0.3)	0.3(0.1)	0.0(0.0)	14.2(14.2)
		4	**44.8**(63.8)	**36.5**(27.0)	16.4(8.8)	2.1(0.4)	0.2(0.0)	0.0(0.0)	0.0(0.0)	18.7(9.2)
	6	6	**40.5**(57.3)	**43.2**(30.5)	14.1(11.1)	1.8(1.1)	0.3(0.1)	0.0(0.0)	0.0(0.0)	16.2(12.3)
		8	**39.5**(53.2)	**46.9**(33.8)	11.8(11.6)	1.5(1.2)	0.3(0.1)	0.1(0.0)	0.0(0.0)	13.7(12.9)
			q_1(0.00)	q_2(0.00)	q_3(0.03)	q_4(0.05)	q_5(0.11)	q_6 (0.33)		
		8	0.0(12.5)	0.3(12.7)	0.6(14.1)	3.8(15.9)	28.9(21.2)	**66.3**(23.6)	33.7(76.4)	0.0(0.0)
	3	12	0.0(8.3)	0.2(8.5)	0.6(9.5)	3.3(11.5)	29.1(23.9)	**66.7**(38.2)	33.3(61.8)	0.0(0.0)
8		16	0.0(6.2)	0.2(6.4)	0.5(7.2)	3.4(9.6)	28.4(25.0)	**67.5**(45.5)	32.5(54.5)	0.0(0.0)
		4	0.0(25.0)	0.0(25.0)	0.1(25.3)	4.8(24.7)	95.1(0.0)	**0.0**(0.0)	100.0(100.0)	0.0(0.0)
	6	6	0.0(16.7)	0.0(16.7)	0.0(16.9)	0.3(17.3)	18.7(18.8)	**80.9**(13.7)	19.1(86.3)	0.0(0.0)
		8	0.0(12.5)	0.0(12.5)	0.0(12.7)	0.2(13.0)	17.6(18.7)	**82.1**(30.6)	17.9(69.4)	0.0(0.0)
			q_1(0.50)	q_2(0.51)	q_3(0.52)	q_4(0.53)	q_5(0.54)	q_6 (0.55)		
		8	93.0(92.1)	5.7(6.9)	1.1(0.9)	0.2(0.2)	0.0(0.0)	0.0(0.0)	0.0(0.0)	100.0(100.0)
	3	12	94.1(92.6)	5.1(6.3)	0.7(0.9)	0.2(0.2)	0.0(0.0)	0.0(0.0)	0.0(0.0)	100.0(100.0)
9		16	93.6(92.4)	5.2(6.3)	0.8(1.1)	0.1(0.2)	0.0(0.0)	0.0(0.0)	0.0(0.0)	100.0(100.0)
		4	95.2(94.0)	4.3(5.5)	0.4(0.5)	0.1(0.0)	0.0(0.0)	0.0(0.0)	0.0(0.0)	100.0(100.0)
	6	6	96.6(94.4)	2.9(4.9)	0.5(0.6)	0.0(0.0)	0.0(0.0)	0.0(0.0)	0.0(0.0)	100.0(100.0)
		8	97.2(95.1)	2.4(4.4)	0.3(0.5)	0.1(0.0)	0.0(0.0)	0.0(0.0)	0.0(0.0)	100.0(100.0)

Although the first dose in Scenario 9 has the probability of toxicity as 0.50, it is recommended in more than 93% of the trials by both the algorithms. Since the toxicity is well above the target γ, this dose should not be recommended as the MTD in a trial. Other than stopping at fixed n, this scenario motivates us to consider an alternative stopping rule, as described in Section 2.3. The simulation results for the proposed stopping rule, obtained when $c = 3$ and $n = 8$, are presented in Table 4. In Scenario 3, no dose (ND) is recommended in 16.6% of the trials by the original algorithm, while this is 12.8% by the modified algorithm. In this scenario, the first two doses has the probabilities of toxicity as 0.30 and 0.40, respectively. Since the first dose is the MTD and also the second dose has higher toxicity probability than the target, the proposed stopping rule has forced often not to recommend any available dose as the MTD.

In Scenario 5, the original version does not recommend any dose as the MTD in 1% of the trials. This figure is negligible as the next dose has very large probability of toxicity (0.90).

No dose is recommended in 13.9% and 12.3% of the time by the successive algorithms in Scenario 7. Here the successive probabilities of toxicity in the first three doses are 0.30, 0.30

Table 2: The percentage distribution of MTD and dose allocation (in parenthesis) obtained for the various choices of cohort size and total cohorts when the modified isotonic design is used. The bold values indicate the recommendation of the true MTD. Note that c and n denote the cohort size and total cohorts, respectively.

Sce.	c	n	Dose Level						Below MTD	Above MTD
			1	2	3	4	5	6		
			q_1(0.05)	q_2(0.10)	q_3(0.20)	q_4(0.30)	q_5(0.50)	q_6 (0.70)		
		8	3.4(17.1)	14.7(24.1)	29.2(28.3)	**36.5**(21.8)	13.8(7.8)	2.4(0.9)	47.3(69.5)	16.2(8.7)
	3	12	3.7(12.6)	14.0(20.6)	30.4(28.3)	**42.2**(28.1)	8.6(9.2)	1.2(1.2)	48.1(61.5)	9.8(10.4)
1		16	3.4(10.2)	14.6(19.4)	31.6(29.0)	**44.7**(31.5)	5.5(8.8)	0.2(1.1)	49.6(58.6)	5.7(9.9)
		4	1.6(26.7)	10.9(29.8)	24.3(29.4)	**38.2**(14.1)	25.0(0.0)	0.0(0.0)	36.8(85.9)	25.0(14.1)
	6	6	1.6(18.3)	10.8(23.7)	27.3(28.0)	**40.2**(21.6)	17.0(7.7)	3.2(0.6)	39.7(70.0)	20.2(8.3)
		8	1.7(14.2)	11.1(20.6)	29.2(27.8)	**45.9**(26.5)	10.8(9.7)	1.3(1.2)	42.0(62.6)	12.1(10.9)
			q_1(0.09)	q_2(0.16)	q_3(0.27)	q_4(0.38)	q_5(0.57)	q_6 (0.75)		
		8	9.3(23.3)	25.2(30.5)	**33.6**(27.8)	24.4(14.6)	6.4(3.5)	1.0(0.3)	34.5(53.8)	31.8(18.4)
	3	12	9.7(18.9)	27.7(29.6)	**36.5**(29.8)	23.4(17.6)	2.4(3.7)	0.3(0.4)	37.4(48.5)	26.1(21.7)
2		16	9.6(16.7)	27.7(28.9)	**39.3**(32.0)	22.2(18.7)	1.0(3.4)	0.1(0.4)	37.3(45.6)	23.3(22.5)
		4	6.2(30.6)	22.7(34.5)	**32.9**(26.6)	28.6(8.3)	9.6(0.0)	0.0(0.0)	28.9(65.1)	38.2(8.3)
	6	6	6.0(22.4)	24.6(30.5)	**35.4**(28.5)	25.5(15.0)	7.6(3.4)	0.8(0.2)	30.6(52.9)	33.9(18.5)
		8	5.6(18.0)	24.0(28.9)	**41.8**(31.2)	24.9(17.6)	3.4(4.0)	0.3(0.3)	29.6(46.9)	28.6(21.9)
			q_1(0.30)	q_2(0.40)	q_3(0.52)	q_4(0.61)	q_5(0.76)	q_6 (0.87)		
		8	**68.5**(69.4)	25.3(24.2)	5.5(5.8)	0.7(0.6)	0.0(0.0)	0.0(0.0)	0.0(0.0)	31.5(30.6)
	3	12	**70.7**(69.4)	24.7(24.4)	4.2(5.5)	0.4(0.7)	0.0(0.0)	0.0(0.0)	0.0(0.0)	29.3(30.6)
3		16	**73.4**(70.3)	24.1(24.1)	2.2(4.9)	0.2(0.6)	0.0(0.0)	0.0(0.0)	0.0(0.0)	26.6(29.7)
		4	**67.1**(71.2)	25.6(23.8)	6.4(4.8)	0.8(0.2)	0.1(0.0)	0.0(0.0)	0.0(0.0)	32.9(28.8)
	6	6	**70.4**(70.2)	24.7(24.2)	4.2(5.2)	0.5(0.4)	0.1(0.0)	0.0(0.0)	0.0(0.0)	29.6(29.8)
		8	**75.1**(71.1)	21.9(23.8)	2.8(4.6)	0.2(0.5)	0.0(0.0)	0.0(0.0)	0.0(0.0)	24.9(28.9)
			q_1(0.00)	q_2(0.00)	q_3(0.04)	q_4(0.09)	q_5(0.25)	q_6 (0.49)		
		8	0.0(12.5)	0.6(12.8)	3.3(15.6)	22.6(22.0)	**47.6**(25.1)	25.9(11.9)	26.5(62.9)	25.9(11.9)
	3	12	0.0(8.3)	0.7(8.9)	2.4(10.9)	23.9(22.5)	**59.0**(34.8)	13.9(14.6)	27.0(50.6)	13.9(14.6)
4		16	0.0(6.2)	0.5(6.6)	2.8(9.1)	23.9(22.8)	**64.2**(41.6)	8.6(13.6)	27.2(44.7)	8.6(13.6)
		4	0.0(25.0)	0.1(25.0)	1.2(25.5)	10.2(24.5)	**88.5**(0.0)	0.0(0.0)	11.5(100.0)	0.0(0.0)
	6	6	0.0(16.7)	0.1(16.7)	0.9(17.3)	19.4(20.6)	**43.8**(20.8)	35.8(7.9)	20.4(71.3)	35.8(7.9)
		8	0.0(12.5)	0.1(12.5)	1.0(13.2)	19.1(20.2)	**62.2**(27.9)	17.7(13.6)	20.2(58.5)	17.7(13.6)
			q_1(0.20)	q_2(0.90)	q_3(0.90)	q_4(0.90)	q_5(0.90)	q_6 (0.90)		
		8	**98.7**(87.8)	1.3(12.2)	0.0(0.0)	0.0(0.0)	0.0(0.0)	0.0(0.0)	0.0(0.0)	1.3(12.2)
	3	12	**99.7**(91.6)	0.3(8.4)	0.0(0.0)	0.0(0.0)	0.0(0.0)	0.0(0.0)	0.0(0.0)	0.3(8.4)
5		16	**99.8**(93.6)	0.2(6.4)	0.0(0.0)	0.0(0.0)	0.0(0.0)	0.0(0.0)	0.0(0.0)	0.2(6.4)
		4	**96.0**(77.2)	4.0(22.8)	0.0(0.0)	0.0(0.0)	0.0(0.0)	0.0(0.0)	0.0(0.0)	4.0(22.8)
	6	6	**98.9**(83.8)	1.1(16.2)	0.0(0.0)	0.0(0.0)	0.0(0.0)	0.0(0.0)	0.0(0.0)	1.1(16.2)
		8	**99.6**(87.6)	0.4(12.4)	0.0(0.0)	0.0(0.0)	0.0(0.0)	0.0(0.0)	0.0(0.0)	0.4(12.4)
			q_1(0.10)	q_2(0.20)	q_3(0.90)	q_4(0.90)	q_5(0.90)	q_6 (0.90)		
		8	16.3(28.0)	**83.1**(61.4)	0.6(10.6)	0.0(0.0)	0.0(0.0)	0.0(0.0)	16.3(28.0)	0.6(10.6)
	3	12	15.4(23.4)	**84.5**(69.2)	0.1(7.3)	0.0(0.0)	0.0(0.0)	0.0(0.0)	15.4(23.4)	0.1(7.4)
6		16	15.2(21.5)	**84.8**(73.0)	0.0(5.5)	0.0(0.0)	0.0(0.0)	0.0(0.0)	15.2(21.5)	0.0(5.5)
		4	11.4(33.4)	**81.9**(47.1)	6.7(19.5)	0.0(0.0)	0.0(0.0)	0.0(0.0)	11.4(33.4)	6.7(19.5)
	6	6	11.4(26.1)	**87.8**(59.4)	0.8(14.5)	0.0(0.0)	0.0(0.0)	0.0(0.0)	11.4(26.1)	0.8(14.5)
		8	10.4(21.8)	**89.1**(67.1)	0.5(11.1)	0.0(0.0)	0.0(0.0)	0.0(0.0)	10.4(21.8)	0.5(11.1)
			q_1(0.30)	q_2(0.30)	q_3(0.50)	q_4(0.50)	q_5(0.50)	q_6 (0.50)		
		8	**50.7**(61.0)	**37.7**(28.4)	8.8(9.1)	2.2(1.3)	0.5(0.2)	0.1(0.0)	0.0(0.0)	11.6(10.6)
	3	12	**50.7**(58.4)	**40.7**(31.1)	6.4(8.5)	1.5(1.5)	0.5(0.3)	0.2(0.1)	0.0(0.0)	8.6(10.5)
7		16	**48.5**(54.7)	**45.0**(35.0)	4.8(8.2)	1.3(1.7)	0.2(0.3)	0.1(0.1)	0.0(0.0)	6.4(10.3)
		4	**44.8**(63.8)	**36.5**(27.0)	16.4(8.8)	2.1(0.4)	0.2(0.0)	0.0(0.0)	0.0(0.0)	18.7(9.2)
	6	6	**48.5**(65.0)	**36.2**(25.5)	13.0(9.0)	2.0(0.4)	0.2(0.0)	0.0(0.0)	0.0(0.0)	15.2(9.5)
		8	**47.0**(56.4)	**44.6**(32.8)	6.8(9.4)	1.2(1.2)	0.2(0.1)	0.1(0.0)	0.0(0.0)	8.3(10.8)
			q_1(0.00)	q_2(0.00)	q_3(0.03)	q_4(0.05)	q_5(0.11)	q_6 (0.33)		
		8	0.0(12.5)	0.3(12.7)	0.7(14.0)	4.5(15.9)	34.6(21.8)	**59.9**(23.2)	40.1(76.8)	0.0(0.0)
	3	12	0.0(8.3)	0.4(8.6)	0.9(9.7)	4.3(11.9)	41.7(27.3)	**52.6**(34.0)	47.4(66.0)	0.0(0.0)
8		16	0.0(6.2)	0.4(6.6)	0.7(7.4)	4.4(10.1)	44.3(31.9)	**50.2**(37.8)	49.8(62.2)	0.0(0.0)
		4	0.0(25.0)	0.1(25.0)	0.2(25.3)	4.4(24.7)	95.4(0.0)	**0.0**(0.0)	100.0(100.0)	0.0(0.0)
	6	6	0.0(16.7)	0.1(16.7)	0.2(17.0)	2.0(17.5)	27.2(18.4)	**70.5**(13.7)	29.5(86.3)	0.0(0.0)
		8	0.0(12.5)	0.1(12.5)	0.3(12.7)	1.8(13.5)	37.6(21.9)	**60.2**(26.9)	39.8(73.1)	0.0(0.0)
			q_1(0.50)	q_2(0.51)	q_3(0.52)	q_4(0.53)	q_5(0.54)	q_6 (0.55)		
		8	95.7(93.3)	3.4(5.8)	0.6(0.9)	0.2(0.1)	0.0(0.0)	0.0(0.0)	0.0(0.0)	100.0(100.0)
	3	12	97.0(94.2)	2.5(4.8)	0.4(0.8)	0.0(0.1)	0.0(0.0)	0.0(0.0)	0.0(0.0)	100.0(100.0)
9		16	97.8(95.1)	1.9(4.0)	0.3(0.7)	0.0(0.1)	0.0(0.0)	0.0(0.0)	0.0(0.0)	100.0(100.0)
		4	96.6(94.3)	2.9(5.1)	0.5(0.5)	0.1(0.0)	0.0(0.0)	0.0(0.0)	0.0(0.0)	100.0(100.0)
	6	6	98.4(95.6)	1.4(3.9)	0.2(0.5)	0.0(0.0)	0.0(0.0)	0.0(0.0)	0.0(0.0)	100.0(100.0)
		8	99.2(96.3)	0.8(3.3)	0.0(0.3)	0.0(0.0)	0.0(0.0)	0.0(0.0)	0.0(0.0)	100.0(100.0)

and 0.50, respectively. The high toxicity probability in the third dose is a potential reason for not recommending any dose in so many trials. In 79.6% of the time, no dose is recommended in Scenario 9, while the figure is 77.7% for the modified algorithm. These happen as the first dose bears the toxicity probability as 0.50. Although not presented here, we have found that if the total cohorts is doubled, i.e. $n = 16$, then no dose recommendations are 6%, 4%, and 84%, respectively for the above mentioned scenarios. That is, wrong decision decreases as n increases. Apart from refraining the wrong dose to be selected as the MTD, the new stopping rule has not altered the results that we obtained in case of fixed n.

Simulation results for the BOIN design are presented in Table 3. Compared to that of the BOIN design, the modified isotonic design minimizes recommending toxic doses as the MTD. However, we cannot achieve this for all the scnearios if the original isotonic design is used

instead. The allocation of toxic doses during trials is also relatively small for the modified

Table 3: The percentage distribution of MTD and dose allocation (in parenthesis) obtained for various choices of cohort size and total cohorts when the BOIN design is used. The bold values indicate the recommendation of the true MTD. Note that c and n denote the cohort size and total cohorts, respectively.

Sce.	c	n	Dose Level						Below MTD	Above MTD
			1	2	3	4	5	6		
			q_1(0.05)	q_2(0.10)	q_3(0.20)	q_4(0.30)	q_5(0.50)	q_6 (0.70)		
		8	0.3 (15.5)	4.8(21.2)	29.1(29.3)	**46.2**(24.0)	18.9(9.1)	0.7(0.9)	34.2(66.0)	19.6(10.0)
	3	12	0.3(10.4)	3.1(15.9)	23.4(27.9)	**55.4**(31.4)	17.3(13.0)	0.4(1.4)	26.8(54.2)	17.7(14.4)
1		16	0.2(7.8)	2.6(12.8)	20.5(26.9)	**61.4**(37.5)	15.1(13.8)	0.1(1.3)	23.3(47.5)	15.2(15.1)
		4	0.1(26.3)	7.6(30.3)	45.8(29.3)	**46.4**(14.1)	0.0(0.0)	0.0(0.0)	53.5(85.9)	0.0(0.0)
	6	6	0.1(17.7)	3.4(22.1)	29.1(28.7)	**52.5**(23.2)	14.7(7.9)	0.1(0.4)	33.6(68.5)	14.8(8.3)
		8	0.2(13.3)	2.2(17.4)	23.7(28.3)	**59.4**(29.8)	14.4(10.4)	0.2(0.8)	26.1(59.0)	14.6(11.2)
			q_1(0.09)	q_2(0.16)	q_3(0.27)	q_4(0.38)	q_5(0.57)	q_6 (0.75)		
		8	1.6(19.5)	16.8(28.8)	**43.9**(31.1)	31.1(16.6)	6.2(3.8)	0.2(0.2)	18.4(48.3)	37.5(20.6)
	3	12	1.2(13.7)	12.8(25.4)	**45.1**(33.8)	35.8(21.4)	4.7(5.3)	0.1(0.4)	14.0(39.1)	40.6(27.1)
2		16	1.0(10.4)	10.8(21.7)	**45.6**(33.6)	39.6(25.7)	2.8(5.3)	0.0(0.3)	11.5(32.1)	42.4(31.3)
		4	2.1(29.5)	22.7(35.0)	**51.9**(26.8)	23.3(8.7)	0.0(0.0)	0.0(0.0)	24.8(64.5)	23.3(8.7)
	6	6	0.8(20.1)	13.9(29.4)	**48.6**(31.3)	33.0(15.9)	3.5(3.2)	0.0(0.1)	14.7 (49.5)	36.5(19.2)
		8	0.7(15.3)	10.8(25.3)	**48.1**(34.8)	37.4(20.5)	2.9(4.0)	0.0(0.1)	11.5(40.6)	40.3(24.6)
			q_1(0.30)	q_2(0.40)	q_3(0.52)	q_4(0.61)	q_5(0.76)	q_6 (0.87)		
		8	**51.5**(62.8)	29.4(28.8)	6.8(7.5)	0.4(0.8)	0.1(0.0)	0.0(0.0)	0.0(0.0)	36.7(37.1)
	3	12	**53.1**(61.7)	29.5(30.0)	4.8(7.3)	0.3(0.9)	0.0(0.1)	0.0(0.0)	0.0(0.0)	34.6(38.3)
3		16	**53.1**(62.4)	29.0(30.0)	3.3(6.8)	0.1(0.7)	0.0(0.0)	0.0(0)0	0.0(0.0)	32.4(37.5)
		4	**59.4**(68.7)	25.7(26.0)	5.0(5.1)	0.3(0.3)	0.0(0.0)	0.0(0.0)	0.0(0.0)	31.0(31.4)
	6	6	**56.7**(66.4)	27.8(27.6)	4.0(5.6)	0.1(0.4)	0.0(0.0)	0.0(0.0)	0.0(0.0)	31.9(33.6)
		8	**57.9**(66.1)	27.6(28.2)	2.8(5.3)	0.1(0.4)	0.0(0.0)	0.0(0.0)	0.0(0.0)	30.5(33.9)
			q_1(0.00)	q_2(0.00)	q_3(0.04)	q_4(0.09)	q_5(0.25)	q_6 (0.49)		
		8	0.0(12.5)	0.0(12.6)	0.3(14.8)	9.4(20.6)	**61.5**(26.4)	28.8(13.1)	9.7(60.5)	28.8(13.1)
	3	12	0.0(8.3)	0.0(8.4)	0.2(10.0)	6.9(17.8)	**65.3**(35.3)	27.5(20.2)	7.1(44.5)	27.5(20.2)
4		16	0.0(6.2)	0.0(6.3)	0.2(7.5)	16.2(15.8)	**71.1**(43.0)	22.5(21.1)	16.4(35.8)	22.5(21.1)
		4	0.0(25.0)	0.0(25.0)	2.2(25.4)	97.8(24.5)	**0.0**(0.0)	0.0(0.0)	2.2(100.0)	0.0(0.0)
	6	6	0.0(16.7)	0.0(16.7)	0.1(17.2)	10.3(21.0)	**68.0**(20.6)	21.6(7.8)	10.4(71.6)	21.6(7.8)
		8	0.0(12.5)	0.0(12.5)	0.0(12.9)	5.5(18.4)	**70.9**(29.1)	23.6(14.5)	5.5(56.4)	23.6(14.5)
			q_1(0.20)	q_2(0.90)	q_3(0.90)	q_4(0.90)	q_5(0.90)	q_6 (0.90)		
		8	**97.4**(85.5)	0.1(14.5)	0.0(0.0)	0.0(0.0)	0.0(0.0)	0.0(0.0)	0.0(0.0)	0.1(14.5)
	3	12	**97.2**(89.8)	0.0(10.2)	0.0(0.0)	0.0(0.0)	0.0(0.0)	0.0(0.0)	0.0(0.0)	0.0(10.2)
5		16	**97.3**(92.2)	0.0(7.8)	0.0(0.0)	0.0(0.0)	0.0(0.0)	0.0(0.0)	0.0(0.0)	0.0(7.8)
		4	**98.2**(77.8)	0.0(22.2)	0.0(0.0)	0.0(0.0)	0.0(0.0)	0.0(0.0)	0.0(0.0)	0.0(22.2)
	6	6	**97.8**(84.3)	0.0(15.7)	0.0(0.0)	0.0(0.0)	0.0(0.0)	0.0(0.0)	0.0(0.0)	0.0(15.7)
		8	**98.0**(87.9)	0.0(12.1)	0.0(0.0)	0.0(0.0)	0.0(0.0)	0.0(0.0)	0.0(0.0)	0.0(12.1)
			q_1(0.10)	q_2(0.20)	q_3(0.90)	q_4(0.90)	q_5(0.90)	q_6 (0.90)		
		8	3.5(22.4)	**96.0**(64.2)	0.2(13.3)	0.0(0.0)	0.0(0.0)	0.0(0.0)	3.5(22.4)	0.2(13.4)
	3	12	3.0(16.8)	**96.7**(73.6)	0.1(9.6)	0.0(0.0)	0.0(0.0)	0.0(0.0)	3.0(16.8)	0.1(9.6)
6		16	2.2(13.1)	**97.7**(79.3)	0.0(7.6)	0.0(0.0)	0.0(0.0)	0.0(0.0)	2.2(13.1)	0.0(7.6)
		4	4.6(31.8)	**95.0**(48.5)	0.2(19.7)	0.0(0.0)	0.0(0.0)	0.0(0.0)	4.6(31.8)	0.2(19.7)
	6	6	2.5(22.7)	**97.3**(62.6)	0.0(14.7)	0.0(0.0)	0.0(0.0)	0.0(0.0)	2.5(22.7)	0.0(14.7)
		8	2.2(17.7)	**97.6**(70.8)	0(11.5)	0.0(0.0)	0.0(0.0)	0.0(0.0)	2.6(17.7)	0.0(11.5)
			q_1(0.30)	q_2(0.30)	q_3(0.50)	q_4(0.50)	q_5(0.50)	q_6 (0.50)		
		8	**35.8**(54.9)	**36.9**(30.4)	13.3(12.6)	2.0(1.9)	0.5(0.2)	0.0(0.0)	0.0(0.0)	15.3(14.7)
	3	12	**34.3**(50.0)	**39.8**(34.4)	11.7(13.2)	1.8(2.1)	0.3(0.3)	0.1(0.1)	0.0(0.0)	13.8(15.6)
7		16	**32.5**(48.0)	**43.3**(36.6)	9.2(12.9)	1.1(1.9)	0.4(0.4)	0.0(0.1)	0.0(0.0)	10.7(15.4)
		4	**45.1**(63.6)	**33.5**(26.7)	10.8(9.1)	0.9(0.6)	0.0(0.0)	0.0(0.0)	0.0(0.0)	11.7(9.7)
	6	6	**39.4**(57.3)	**37.8**(30.6)	10.5(10.9)	0.9(1.1)	0.1(0.1)	0.0(0.0)	0.0(0.0)	11.5(12.1)
		8	**37.3**(54.1)	**41.5**(33.6)	8.6(11.0)	0.9(1.2)	0.1(0.1)	0.0(0.0)	0.0(0.0)	9.6(12.3)
			q_1(0.00)	q_2(0.00)	q_3(0.03)	q_4(0.05)	q_5(0.11)	q_6 (0.33)		
		8	0.0(12.5)	0.0(12.6)	0.0(13.9)	1.1(15.4)	28.5(20.9)	**70.4**(24.6)	29.6(75.4)	0.0(0.0)
	3	12	0.0(8.3)	0.0(8.4)	0.0(9.3)	0.4(10.6)	19.8(23.0)	**79.7**(40.5)	20.2(59.5)	0.0(0.0)
8		16	0.0(6.2)	0.0(6.3)	0.0(7.0)	0.3(8.0)	18.9(24.0)	**80.7**(48.5)	19.2(51.5)	0.0(0.0)
		4	0.0(25.0)	0.0(25.0)	1.2(25.3)	98.8(24.7)	0.0(0.0)	**0.0**(0.0)	100.0(100.0)	0.0(0.0)
	6	6	0.0(16.7)	0.0(16.7)	0.0(16.9)	0.9(17.6)	32.4(18.4)	**66.7**(13.8)	33.3(86.2)	0.0(0.0)
		8	0.0(12.5)	0.0(12.5)	0.0(12.7)	0.3(13.3)	19.3(20.6)	**80.5**(28.4)	19.3(71.6)	0.0(0.0)
			q_1(0.50)	q_2(0.51)	q_3(0.52)	q_4(0.53)	q_5(0.54)	q_6 (0.55)		
		8	**29.0**(86.9)	3.3(10.9)	0.9(1.9)	0.1(0.2)	0.0(0.0)	0.0(0.0)	0.0(0.0)	33.3(100.0)
	3	12	**20.2**(87.4)	2.1(10.4)	0.4(2.0)	0.0(0.2)	0.0(0.0)	0.0(0.0)	0.0(0.0)	22.7(100.0)
9		16	**13.9**(87.7)	1.1(10.2)	0.3(1.9)	0.0(0.3)	0.0(0.0)	0.0(0.0)	0.0(0.0)	15.3(100.0)
		4	**32.1**(91.4)	2.3(7.8)	0.4(0.8)	0.0(0.0)	0.0(0)	0.0(0.0)	0.0(0.0)	34.8(100.0)
	6	6	**21.9**(91.4)	1.7(7.6)	0.3(1.0)	0.0(0.0)	0.0(0.0)	0.0(0.0)	0.0(0.0)	23.9(100.0)
		8	**14.2**(91.6)	1.1(7.5)	0.1(0.9)	0.0(0.0)	0.0(0.0)	0.0(0.0)	0.0(0.0)	15.4(100.0)

design. Since the BOIN design uses a rule to stop early for excessive toxicity, we have found a good percentage of trials not to recommend an MTD on some occasions. In particular, 11.9, 2.5, 11.5 and 66.7 percent trials do not recommend any dose as the MTD, if $n = 8$ in the Scenarios 3, 5, 7 and 9. These values are quite comparable with the values obtained for our proposed stopping rule applied to the modified isotonic design: see Table 4. However, our stopping rule refrains from reccomeding any MTD in 77.7 percent of the trials compared to 66.7 percent obtained by the BOIN in Scenario 9. Since this scenario does not have a true MTD, our design is performing well over the BOIN design. For most of the scenarios, the correct identification of the MTD is more in the BOIN compared to those in the isotonic and modified isotonic designs. Since the BOIN stops for excessive toxicity, the accuracy in the identification of true MTD decreases for the Scenarios 3, 5 and 7 compared to the other two

designs. Since these scenarios have the true MTD towards the beginning of the dose region, they are often stopped with no dose recommendation. As Scenario 9 has no true MTD, the BOIN recommends no dose as the MTD in majority of the trials, whereas the original and modfied isotonic designs fail to do so unless our proposed stopping rule is used.

Table 4: Impact of the proposed stopping rule on the original and modifed isotonic designs. The percentage distribution of MTD and dose allocation (in parenthesis) for the scenarios when $c = 3$ and $n = 8$. The ND is the percentage of trials that dose not recommended any dose as the MTD.

		Dose level						
Sce.	Design	1	2	3	4	5	6	ND
1		0.05	0.10	0.20	0.30	0.50	0.70	
	Original	3.1(17.1)	10.7(22.6)	25.3(28.1)	**39.2**(22.8)	18.7(8.4)	3.0(1.0)	0.0
	Modified	3.5(17.2)	14.6(23.9)	28.3(28.1)	**35.5**(21.7)	15.2(8.1)	3.0(1.0)	0.0
2		0.09	0.16	0.27	0.38	0.57	0.75	
	Original	7.4(22.4)	19.6(29.0)	**35.2**(29.3)	28.1(15.4)	8.4(3.7)	1.2(0.3)	0.0
	Modified	9.5(23.6)	26.0(30.5)	**33.4**(27.7)	23.6(14.4)	6.5(3.5)	0.0(0.3)	0.0
3		0.30	0.40	0.52	0.61	0.76	0.87	
	Original	**46.2**(65.1)	27.4(27.3)	8.6(6.8)	1.2(0.7)	0.1(0.1)	0.0(0.0)	16.6
	Modified	**55.2**(69.4)	25.2(24.1)	6.1(5.8)	0.8(0.7)	0.0(0.0)	0.0(0.0)	12.8
4		0.0	0.0	0.04	0.09	0.25	0.49	
	Original	0.0(12.5)	0.5(12.8)	2.0(15.1)	16.8(21.6)	**48.1**(25.8)	32.6(12.3)	0.0
	Modified	0.0(12.5)	0.6(12.9)	2.5(15.2)	23.2(22.4)	**47.1**(25.1)	26.6(11.9)	0.0
5		0.20	0.90	0.90	0.90	0.90	0.90	
	Original	**97.8**(87.7)	1.2(12.3)	0.0(0.0)	0.0(0.0)	0.0(0.0)	0.0(0.0)	1.0
	Modified	**97.2**(87.8)	1.4(12.1)	0.0(0.0)	0.0(0.0)	0.0(0.0)	0.0(0.0)	1.4
6		0.10	0.20	0.90	0.90	0.90	0.90	
	Original	10.4(25.1)	**87.9**(63.9)	1.4(11.0)	0.0(0.0)	0.0(0.0)	0.0(0.0)	0.4
	Modified	15.9(27.6)	**83.3**(61.7)	0.7(10.7)	0.0(0.0)	0.0(0.0)	0.0(0.0)	0.0
7		0.30	0.30	0.50	0.50	0.50	0.50	
	Original	**32.0**(58.4)	**36.8**(29.2)	13.5(10.6)	3.1(1.6)	0.5(0.2)	0.2(0.0)	13.9
	Modified	**39.2**(61.6)	**36.0**(27.7)	9.6(9.1)	2.1(1.4)	0.6(0.2)	0.0(0.0)	12.3
8		0.0	0.0	0.03	0.05	0.11	0.33	
	Original	0.0(12.5)	0.3(12.7)	0.9(14.1)	3.6(15.8)	28.5(21.3)	**66.7**(23.7)	0.0
	Modified	0.0(12.5)	0.3(12.7)	0.8(14.0)	4.1(15.7)	33.9(21.6)	**60.9**(23.6)	0.0
9		0.50	0.51	0.52	0.53	0.54	0.55	
	Original	15.5(91.5)	3.5(7.3)	1.2(1.1)	0.1(0.1)	0.1(0)	0.0(0.0)	**79.6**
	Modified	18.2(93.2)	3.2(5.8)	0.7(0.9)	0.1(0.1)	0.0(0.0)	0.0(0.0)	**77.7**

5. Discussion

This paper has made a detailed investigation of the isotonic design. For a given cohort size, the percentage of correct identification of the MTD increases, as the total cohorts increase. Designs with cohort size 6 can identify the MTD more accurately than those with cohort size 3. Cohort size 6 with total cohorts 4 has the problem in identifying the MTD for Scenarios 4 and 8. Due to small number of total cohorts, all the trials ended before reaching the highest dose level in these scenarios. Therefore, we suggest considering the total number of cohorts to be more than the number of dose levels.

The percentage of dose allocation at the true MTD also increases in most of the cases if n increases. The modified isotonic design has been found to limit toxic doses to appear as the MTD. Also, in some scenarios, it can identify the MTD more accurately than the original design. As a whole, cohort size and total cohorts has impact on the isotonic design. As seen through the numerical findings, an increase in either of these two can lead to more accurate identification of the MTD.

Although all the toxicity probabilities in Scenario 9 are higher than the target rate, the original algorithm recommends an MTD at the end of each trial. This aspect of the design is not ethically attractive and therefore, we have proposed an alternative stopping rule. The suggested rule can refrain trials from recommending an MTD, when none of the available doses is eligible to be MTD.

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