**On Performance of the 3+3 Design and its Modified Versions for Dose Finding in Phase I Clinical Trials**

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*Abstract: Phase I clinical trial is the first step of testing drugs in humans. Clinicians often use the rule-based traditional 3+3 design to find the maxi- mum tolerated dose. Since the design has many potential limitations, some modified versions of it are available in the literature to tackle those. How- ever, no explicit comparison of these modified designs exist. In addition of comparing these designs among themselves, this paper also compares them with the model-based continual reassessment method. This is to see whether the modified versions can make a real difference with the original 3+3 design. Also, we would like to see how the modified versions work in comparison with the model-based continual reassessment method. Simulation studies show that all these rule-based designs do not differ much among themselves and also perform poorly compared to the continual reassessment method.*

*Key words: Dose finding studies, phase I trial, maximum tolerated dose, 3+3 design, continual reassessment method.*

1. Introduction

Phase I clinical trials are designed to assess safety, tolerability and pharma- cokinetics of a drug. They are usually small, single-arm and open-label. For nontoxic agents, phase I trials may start with healthy volunteers. But for cyto- toxic agents in cancer treatment, phase I trial starts with the patients for whom standard treatments have failed. For cytotoxic agents, the highest possible dose is searched, since the benefit of treatment is believed to increase with dose. Since toxicity also increases with dose, the challenge is find a dose that will not expose patients to toxicity above the acceptable level. Such a dose is known as the max- imum tolerated dose (MTD).

Since the future of a drug solely depends on the early phases, a careful ap- proach is essential for dose escalation. A phase I design should be able to identify the MTD accurately without exposing many patients to either subtherapeutic or toxic doses. The designs for phase I are usually classified into two broad cat- egories: rule-based and model-based. The essence of the rule-based designs is that they use some pre-specified rules to allocate doses to the patients. On the contrary, the model-based designs assume parametric model and utilise all the available responses to select a dose for the next patient. Some commonly used rule-based designs include the 3+3 design, Storer’s up-an-down designs (Storer, 1989), accelerated titration design (Simon et al., 1997), pharmacologically guided dose-escalation design (Collins et al., 1990), design using isotonic regression (Le- ung and Wang, 2001), etc. The model-based designs include the continual re- assessment method (O’Quigley et al., 1990), escalation with overdose control (Babb et al., 1998), etc. Although the designs above mostly talk about finding the MTD in cancer treatments, they are equally applicable to the non-cancer drugs.

Although the model-based designs have strong properties, sometimes they get less attention by the clinicians. According to Kairalla et al. (2012), logistic difficulties and regulatory concern often limit the use of adaptive model-based designs. Ji and Wang (2013) developed the modified toxicity probability interval (mTPI) design, which with matched sample sizes, has lower risks of exposing patients with highly toxic doses than the 3+3 design. Also, mTPI design is more able to identify the MTD than the 3+3 design. Chiuzan et al. (2015) developed a likelihood-based approach for calculating the operating characteristics of the 3+3 design. The approach allows consistent inferences to be made at each dose level, and evidence to be quantified regardless of cohort size. The method is equally applicable to any design using algorithmic dose-finding rules. Boonstra et al. (2015) numerically investigated the 3+3 and the continual reassessment method to quantify how many patients are assigned to the true MTD using a 10 to 20 patient dose expansion cohort. They also found that such an expansion could improve the identification of the true MTD substantially. Singh et al. (2010) utilised a Bayesian logistic random effects model to analyze the data from a clin- ical trial. Liu and Dey (2015) developed a method for determining sample size when comparing the means in clinical trials. The essence of the method is that it does not require the pre-estimation of variation from an external pilot study.

Le Tourneau et al. (2009) discussed some modified versions of the 3+3 design. It is not clear from their discussion whether these modified versions work well over the 3+3 design. Although the continual reassessment method was compared with the 3+3 design by many authors, it is yet to be compared with the modified versions of the 3+3 design. In this paper, we compare the 3+3 design with its modified versions to find the MTD. These rule-based designs are also compared with the model-based continual reassessment method. The remainder of this pa- per is organised as follows. Section 2 describes the 3+3 design and its variations. The continual reassessment method is introduced in Section 3. Section 4 discusses the settings of simulation study. Simulation results comparing all the designs are presented in Section 5. Finally, the conclusion appears in Section 6.

1. Traditional 3+3 Design and the Modifted Versions

As mentioned in the previous section, the 3+3 is a traditional rule-based de- sign to find the MTD in a phase I clinical trial. Starting with a pre-specified set of doses X = {x(1), . . . , x(d)}, the 3+3 design first assigns the lowest dose x(1) to a cohort of three patients. Escalation to dose x(2) is carried out if none of the three patients experiences toxicity. The trial stops if at least two of the three patients have toxicities. The same dose x(1) is given to three additional patients if one of the initial three patients has a toxic response. Then, if only one of the six patients has toxicity, escalation to dose x(2) is made; otherwise, the trial stops. In such a design, the MTD is usually defined as the highest dose at which the observed toxicity rate is no more than 1/3. Some researchers claim that the MTD should be the dose at which 2 or fewer toxicities in six patients are observed. Therefore, it is recommended to check exactly six patients at the MTD, which may sometimes require a single de-escalation in the 3+3 design.

Simplicity of implementation and safety concerns made the 3+3 design very popular among the clinicians. The design can also provide some data on inter- patient variability in pharmacokinetics, as the same dose is assigned to a cohort of patients at each stage of a trial. However, in this design only information from the current cohort is used to determine dose for the next cohort. The de- sign is inefficient when the starting dose is very low and the dose increment is moderate. In such a case, the design requires an excessive number of steps to reach the desired dose. This in turn means that many patients are treated at subtherapeutic doses and very few patients receive doses at or near the MTD. Also, the maximum probability of toxicity that the MTD can have is fixed once the definition is set. For instance, if we define the MTD as the dose at which 2 or fewer toxicities are observed in six patients, then the toxicity rate at that dose is less than or equal to 0.33. So, we cannot find a MTD for any other choice of target toxicity rate in the 3+3 design.

Some modified versions of the design, such as 2+4 and 3+3+3 are also avail- able to accelerate the dose escalation (Le Tourneau et al., 2009). In the 2+4 design, an additional cohort of size 4 is added if one of the two individuals in the first cohort shows toxicity. The same stopping rule as the traditional 3+3 design is followed here. In the 3+3+3 design, the same dose is applied to an additional cohort of size 3 if two individuals in the first two cohorts experience toxicity. The trial stops if three or more individuals in three cohorts show toxicity. Although the modified versions are aimed at accelerating the dose escalation, it is not clear from the discussion in the paper whether they are completely better than the con- servative 3+3 approach or even which is best out of all these modified versions. No explicit comparison of the designs is available elsewhere too.

1. Continual Reassessment Method

The continual reassessment method (CRM) (O’Quigley et al., 1990) is a model-based approach for dose finding in phase I clinical trials. In contrast to the 3+3 design, the method is capable to identify the MTD for any choice of the target toxicity rate. Although the design initially carried out under the Bayesian framework, frequentist extension to it is also available and is known as the continual reassessment maximum likelihood (CRML) method (O’Quigley and Shen, 1996). Both the methods are capable to produce similar results. The use of CRML needs enough dose-response data to facilitate the maximum likelihood estimation of the parameters. It is possible to implement the method after accu- mulating information by either a rule-based design or CRM. As at early stages of a trial data remains small, it is convenient to implement a design under the Bayesian framework. Therefore, we plan to use the CRM in this paper.

The initial CRM characterises the dose-toxicity relationship by simple one- parameter parametric models, such as the hyperbolic tangent model, logistic model, or the power model. In practical situations, the choice of a model is usually elicited from experts familiar with drug development. A one-parameter model is easy to implement but may not depict the dose-response relationship accurately. Since the paper is intended to illustrate the methodology, the choice of a model carries little importance here. A logistic model is often preferred because of its appealing S-shaped description of the dose-toxicity relationship. Here we employ a two-parameter logistic model as shown below.

where θ = (θ1, θ2) is the vector of dose-response parameters and x is the dose given to a patient. The parameter θ2 is restricted to taking positive values to ensure increasing dose-toxicity relationship. The original design starts by allo- cating the initial guess of the MTD to the first patient. The dose to the each successive patient is allocated according to the optimisation criterion to be dis cussed below. Assume that we are at the kth stage in a trial, which means that k patients have been treated with different doses from X . Let x be a k × 1 dose vector with components xl and let r be a k × 1 outcome vector with rl as the lth row (l = 1, . . . , k) representing the toxic outcomes obtained from a patient.

Then the likehood function at the stage k can be written as

Since the available information at the early stages of a trial is small, the design employs Bayesian approach to estimate the dose-response parameters θ. The posterior means of the components of θ = (θ1, θ2) at the kth stage are obtained as

, i=1,2,

where Θ is the parameter space and g(θ) is the prior distribution of the param- eters. For simplicity and rapid numerical computation of the posterior means, a bivariate uniform density is assumed for the joint distribution of the parameters.

The choice of u1 < θ1 < u2 and u3 < θ2 < u4, gives a restricted parameter space as Θ˜ = {θ : u1 < θ1 < u2, u3 < θ2 < u4} so that

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The probability of toxicity at each dose is updated at the end of stage k as

That dose is chosen for the next patient for which the absolute difference between the updated estimate of probability of toxicity and the target toxicity rate γ is minimum. That is,

The trial continues until a fixed sample size n is achieved and the MTD is taken as the dose that would be allocated to patient n + 1 if he were in the trial. The CRM has many salient features. For instance, it treats more patients at doses near the MTD and hence reduces the number of patients treated at low or ineffective dose levels. It utilises all the available data to fit the dose-toxicity curve. However, the dose assignment may be too aggressive. Success of a trial utilising the CRM depends on proper choice of a dose-response model and the prior distribution of the parameter(s). Unlike the rule-based designs, a computer program is in need to implement this design.

The CRM was not well-accepted in its original form due to safety consid- erations, as it could expose patients to unacceptably toxic doses. Consequently, modifications to the CRM were proposed to add additional safety measures, which are discussed in Le Tourneau et al. (2009). Two of the modifications are included in this paper: starting the trial with the lowest dose and increasing the dose by not more than one pre- specified level at a time.

1. Simulation Settings

We have six dose-response scenarios to investigate in Figure 1. As we move from Scenario 1 to 4, the steepness in the dose-toxicity curve decreases. Each scenario has the set of six available doses as X = {1, 3, . . . , 11}. The acceptable level of probability of toxicity γ is assumed to be 0.33. Doses 3, 5, 7 and 11 are the true MTDs in the first four scenarios. The last two scenarios are slightly different in the way that the true MTD is not available in X . That is, the doses at which probabilities of toxicities are equal to the target, are in the mid way of two available doses in X . Such a set of doses is not very unlikely to appear in the real trials. As indicated in the previous section, the uniform prior distribution is used for the parameters θ. More specifically, we consider a single parameter space Θ˜ = {θ : − 4.3 < θ1 < −2.3, 0 < θ2 < 1} for all the scenarios. This parameter space has been chosen, as it has been found to allow a wide range of dose-response scenarios, including the assumed ones. For instance, if we choose values at the lower end, like θ1 = −4.2 and θ1 = 0.1, we get a toxicity curve, where the probabilities at various doses are almost zero. Similarly if we choose values at the upper end, like θ1 = −2.4 and θ1 = 0.99, the toxicity probabilities at the early doses are very high. So the interval that we consider as prior is wide enough to include extreme dose-response scenarios. We can think of using other priors such as beta(1,1) or beta-binomial distribution, since beta distribution is a conjugate prior distribution of the binomial distribution. The beta(1,1) essen- tially leads to a constant value for the probability distribution, something similar to the uniform distribution case. Similar things happens with the beta-binomial distribution. Since such priors are eventually similar to the uniform distribution, we can expect similar results like here in those cases. Following the assignment of a dose to a patient, the binary response is generated using the true probability of toxicity at that dose.

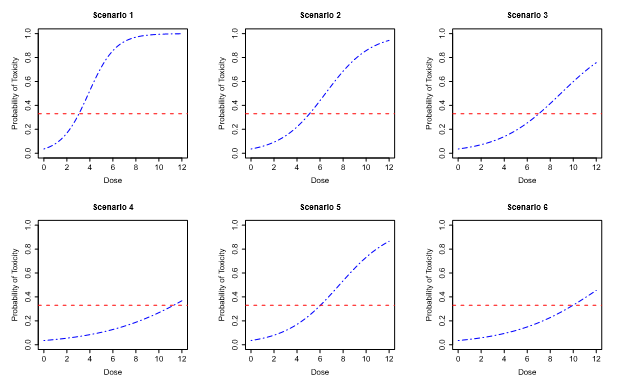
The 3+3 design and its modified versions are compared with the CRM for varying values of n and it includes 15,27,36 and 48. Notice that the numbers are

Figure 1: Dose-response scenarios for simulation study. The respective parameter values are: Scenario 1, ϑ = (−3.3, 0.85);Scenario 2, ϑ = (−3.3, 0.51); Scenario3, ϑ = (−3.3, 0.37); Scenario 4, ϑ = (−3.3, 0.23); Scenario 5, ϑ = (−3.3, 0.43);and Scenario 6, ϑ = (−3.3, 0.26).

The dotted line indicates the target toxicity rate.

all multiple of 3, as 3+3 design and its modified versions utilise a maximum of 6 or 9 patients at each stage to decide on a dose. The CRM stops after reaching n while the other designs may stop early if they already have found the MTD. Sometimes they may fail to identify the MTD even after reaching n. A trial then stops without any dose recommended for the next phase. Each of the six scenarios is investigated through 1000 simulated trials and a self written code in R is used to produce the results.

1. Simulation Findings

The true MTD in the first scenario is 3. When n = 15, the designs 3+3, 2+4 and 3+3+3 can identify the true MTD in 25.3%, 22.1% and 19.6% of the trials, respectively. The CRM can identify the dose 3 correctly in 93.4% of the trials. The identification of the MTD does not change much, as n increases in the 3+3 and 2+4 designs. However, identification improves for the 3+3+3 design. As n increases, the correct identification of the MTD also increases for the CRM. The rule-based designs do not treat that many patients at the MTD. However, majority of the patients are treated at the MTD during the trials in the CRM.

Scenario 2 gets dose 5 as the true MTD. This dose is recommended in 60.8% of the trials by the CRM. The corresponding percentages for the rule-based de- signs are much smaller than this figure. Unlike the first scenario, the CRM is less efficient here in finding the MTD and it is because of the location of the MTD. Fifteen patients probably is not enough to learn the dose-response relationship much accurately in this scenario. As n increases, the correct identification of the MTD increases for the rule-based designs and so does for the CRM. The 3+3 design is more efficient in finding the MTD than the other two rule-based de- signs. Of the rule-based designs, the 3+3+3 design exposes less patients to the subtherapeutic doses. However, it exposes relatively more patients to the toxic doses.

Dose 7 is the true MTD in Scenario 3. If n moves from 15 to 27, the im- provement in the MTD selection is notable for the rule-based designs. However, the changes in response to the other values of n are not that appreciable for the rule-based designs. On the contrary, as n increases, the identification of the MTD increases quite appreciably for the CRM. The number of patients treated at the MTD in the rule-based designs is not as good as that of the CRM.

It is important to mention that as our rule-based designs can stop without recommending a MTD, the total percentage of the MTDs at each row in Tables 1-6 does not make 100. But the total percentage of the patients is always 100 for the rule-based designs, since only allocated doses in the simulated trials are considered in the calculation.

The traditional designs perform worst in Scenario 4. Many trials recommend subtherapeutic doses as the MTD in the 3+3 and 2+4 designs. The 3+3+3 de- sign does not recommend lower doses as the MTD many times, but it fails to identify the MTD accurately. The designs may stop without a MTD because of the restriction in n. Perhaps more recruitment of patients in the trials could lead to a improved identification of the MTD. The CRM is still doing very well even with the recruitment of 15 patients.

The next two scenarios diﬀer from the rest in the way that the true MTD is not available in the dose vectorX. Investigating the behavior of a design for these scenarios is important, as they are likely to happen in reality. The true MTD is 6 in Scenario 5 and it lies between 5 and 7. These two doses are identified as the MTD in most of the trials by the CRM. The rule-based designs are not working as well as the CRM.

In the last scenario, the true MTD lies between doses 9 and 11. For the CRM, these doses are selected as the MTD in 29.3% and 44.1% of the trials, respectively. The selection of the MTD by the other designs are not as good as the CRM. The traditional designs completely fail to identify the MTD if n is 15. However, if we increase the number of patients, the designs become more able to identify the MTD.

For the various scenarios, it is clear that subtherapeutic doses appear as the MTD in the 3+3 design in more than half of the trials. Similar thing happens with the 2+4 design. The 3+3+3 design is much better than the 3+3 and 2+4 designs in this aspect. The CRM is the best in the way that it limits the occurrence of subtherapeutic doses as the MTD considerably. Of all the rule based designs, highly toxic doses appear as the MTD most often in the 3+3+3 design. So the 3+3 and 2+4 are more conservative approaches than the 3+3+3 design. The CRM can identify the MTD more accurately than the considered rule-based designs. Also, it appreciably limits the occurrence of toxic doses as the MTD.

1. Conclusion

The whole purpose of this paper was to investigate the performance of the 3+3 design compared to that of its modified versions. To explore the differences, some plausible dose-response scenarios have been studied in great detail. These rule-based designs are also compared with the model-based CRM. The CRM has been found to work nicely in Scenario 1. For small number of patients, the 3+3 design is better than the other two rule-based designs. But when we are con- sidering large number of patients then the 3+3+3 design is doing comparatively better than 3+3 and 2+4 designs. In the second scenario, the CRM is doing the best. There is not much difference across the traditional designs. The CRM is working nicely in the remaining scenarios as well. We have seen that as the true MTD moves to the upper end of dose region, the correct identification of the MTD gradually decreases both for the CRM and the rule-based designs.

The future of an investigational drug depends on the correct identification of the MTD. Although the 3+3 design and its modified versions are easy to implement, they behave very similarly. So not much improvement over the 3+3 design is possible by the modified versions. Also, the modified designs do not have more attractive properties than the CRM. The CRM is a model-based approach and it utilises all the available information to decide on a dose level. Of course the accuracy of the CRM depends on the location of the MTD. The CRM is much more capable in the identification of the MTD than the modified versions of the 3+3 design. To conclude, the findings in the paper can make the investigators careful in using the modified 3+3 designs.

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**Appendix A: Simulation Resu**

Table 1: The MTD selection and dose allocation for Scenario 1.

Dose

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | | | 1 | 3 | 5 | 7 | 9 | 11 |
| n | Design | Toxicity probability : | 0.08 | 0.32 | 0.72 | 0.93 | 0.99 | 1 |
| 15 | 3+3 | % patients | 39.5 | 47.6 | 12.7 | 0.2 | 0.0 | 0.0 |
|  |  | % MTD | 37.1 | 25.3 | 1.7 | 0.0 | 0.0 | 0.0 |
| 27 | 3+3 | % patients | 35.1 | 48.9 | 15.7 | 0.3 | 0.0 | 0.0 |
|  |  | % MTD | 49.2 | 27.1 | 1.1 | 0.0 | 0.0 | 0.0 |
| 36 | 3+3 | % patients | 33.1 | 49.5 | 17.0 | 0.4 | 0.0 | 0.0 |
|  |  | % MTD | 53.5 | 26.0 | 0.4 | 0.0 | 0.0 | 0.0 |
| 48 | 3+3 | % patients | 31.7 | 50.5 | 17.5 | 0.3 | 0.0 | 0.0 |
|  |  | % MTD | 55.7 | 24.8 | 0.8 | 0.0 | 0.0 | 0.0 |
| 15 | 2+4 | % patients | 37.1 | 45.5 | 16.7 | 0.8 | 0.0 | 0.0 |
|  |  | % MTD | 21.2 | 22.1 | 0.7 | 0.0 | 0.0 | 0.0 |
| 27 | 2+4 | % patients | 34.8 | 46.8 | 17.6 | 0.8 | 0.0 | 0.0 |
|  |  | % MTD | 49.1 | 23.4 | 1.2 | 0.0 | 0.0 | 0.0 |
| 36 | 2+4 | % patients | 33.4 | 46.1 | 19.4 | 1.0 | 0.0 | 0.0 |
|  |  | % MTD | 53.7 | 22.7 | 0.3 | 0.0 | 0.0 | 0.0 |
| 48 | 2+4 | % patients | 31.9 | 45.9 | 21.2 | 1.0 | 0.0 | 0.0 |
|  |  | % MTD | 54.9 | 22.7 | 0.5 | 0.0 | 0.0 | 0.0 |
| 15 | 3+3+3 | % patients | 27.4 | 52.0 | 20.2 | 0.4 | 0.2 | 0.0 |
|  |  | % MTD | 6.4 | 19.6 | 11.2 | 0.0 | 0.0 | 0.0 |
| 27 | 3+3+3 | % patients | 21.5 | 50.3 | 27.5 | 0.7 | 0.0 | 0.0 |
|  |  | % MTD | 26.3 | 30.3 | 11.4 | 0.2 | 0.0 | 0.0 |
| 36 | 3+3+3 | % patients | 19.3 | 49.4 | 30.5 | 0.8 | 0.0 | 0.0 |
|  |  | % MTD | 32.0 | 31.7 | 12.9 | 0.2 | 0.0 | 0.0 |
| 48 | 3+3+3 | % patients | 16.5 | 50.6 | 32.1 | 0.8 | 0.0 | 0.0 |
|  |  | % MTD | 34.5 | 33.4 | 13.8 | 0.2 | 0.0 | 0.0 |
| 15 | CRM | % patients | 6.86 | 75.71 | 15.33 | 1.98 | 0.0 | 0.12 |
|  |  | % MTD | 0.8 | 93.4 | 5.8 | 0.0 | 0.0 | 0.0 |
| 27 | CRM | % patients | 4.1 | 85.24 | 9.48 | 1.11 | 0.007 | 0.06 |
|  |  | % MTD | 0.3 | 98.3 | 1.4 | 0.0 | 0.0 | 0.0 |
| 36 | CRM | % patients | 3.1 | 88.37 | 7.65 | 0.8 | 0.003 | 0.04 |
|  |  | % MTD | 0.7 | 98.5 | 0.8 | 0.0 | 0.0 | 0.0 |
| 48 | CRM | % patients | 2.28 | 91.22 | 5.84 | 0.63 | 0.006 | 0.03 |
|  |  | % MTD | 0.1 | 99.8 | 0.1 | 0.0 | 0.0 | 0.0 |

Table 2: The MTD selection and dose allocation for Scenario 2.

Dose

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  | 1 | 3 | 5 | 7 | 9 | 11 |
| n | Design | Toxicity probability : | 0.06 | 0.15 | 0.32 | 0.57 | 0.78 | 0.91 |
| 15 | 3+3 | % patients | 27.4 | 35.2 | 29.3 | 7.8 | 0.3 | 0.0 |
|  |  | % MTD | 11.4 | 23.5 | 17.9 | 1.3 | 0.0 | 0.0 |
| 27 | 3+3 | % patients | 20.4 | 31.3 | 34.2 | 13.2 | 0.9 | 0.0 |
|  |  | % MTD | 18.8 | 37.2 | 23.3 | 4.2 | 0.1 | 0.0 |
| 36 | 3+3 | % patients | 17.8 | 30.0 | 35.7 | 15.2 | 1.3 | 0.0 |
|  |  | % MTD | 18.7 | 41.3 | 26.5 | 3.7 | 0.0 | 0.0 |
| 48 | 3+3 | % patients | 15.9 | 28.0 | 37.4 | 17.2 | 1.5 | 0.0 |
|  |  | % MTD | 21.9 | 40.2 | 26.8 | 3.8 | 0.1 | 0.0 |
| 15 | 2+4 | % patients | 29.6 | 33.8 | 28.8 | 7.8 | 0.0 | 0.0 |
|  |  | % MTD | 4.7 | 11.1 | 10.3 | 0.0 | 0.0 | 0.0 |
| 27 | 2+4 | % patients | 20.8 | 29.9 | 31.7 | 15.3 | 2.2 | 0.1 |
|  |  | % MTD | 14.2 | 31.8 | 19.4 | 5.0 | 0.1 | 0.0 |
| 36 | 2+4 | % patients | 19.5 | 28.3 | 32.9 | 16.9 | 2.3 | 0.1 |
|  |  | % MTD | 21,0 | 35.6 | 22.2 | 3.8 | 0.2 | 0.0 |
| 48 | 2+4 | % patients | 18.8 | 27.6 | 33.8 | 17.5 | 2.2 | 0.1 |
|  |  | % MTD | 25.3 | 39.4 | 23.3 | 1.5 | 0.1 | 0.0 |
| 15 | 3+3+3 | % patients | 24.1 | 31.6 | 33.6 | 10.5 | 0.3 | 0.0 |
|  |  | % MTD | 1.0 | 2.7 | 12.8 | 7.9 | 0.0 | 0.0 |
| 27 | 3+3+3 | % patients | 14.6 | 20.9 | 35.9 | 26.1 | 2.5 | 0.0 |
|  |  | % MTD | 3.7 | 12.2 | 23.1 | 19.8 | 2.0 | 0.0 |
| 36 | 3+3+3 | % patients | 12.1 | 18.0 | 34.3 | 31.8 | 3.8 | 0.0 |
|  |  | % MTD | 7.4 | 17.7 | 24.2 | 22.7 | 3.0 | 0.0 |
| 48 | 3+3+3 | % patients | 10.5 | 15.8 | 34.0 | 34.9 | 4.7 | 0.1 |
|  |  | % MTD | 10.4 | 22.6 | 27.4 | 20.8 | 3.1 | 0.1 |
| 15 | CRM | % patients | 6.67 | 28.93 | 44.29 | 16.25 | 1.58 | 2.29 |
|  |  | % MTD | 0.0 | 24.7 | 60.8 | 13.9 | .4 | 0.2 |
| 27 | CRM | % patients | 3.70 | 25.69 | 53.93 | 14.23 | 1.12 | 1.34 |
|  |  | % MTD | 0.0 | 20.3 | 71.6 | 8.0 | .1 | 0.0 |
| 36 | CRM | % patients | 2.78 | 23.01 | 59.15 | 13.10 | 0.95 | 1.00 |
|  |  | % MTD | 0.0 | 15.5 | 78.1 | 6.4 | 0.0 | 0.0 |
| 48 | CRM | % patients | 2.08 | 21.77 | 64.69 | 10.01 | 0.68 | 0.76 |
|  |  | % MTD | 0.0 | 13.5 | 82.8 | 3.7 | 0.0 | 0.0 |

Table 3: The MTD selection and dose allocation for Scenario 3.

Dose

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  | 1 | 3 | 5 | 7 | 9 | 11 |
| n | Design | Toxicity probability : | 0.05 | 0.10 | 0.19 | 0.33 | 0.51 | 0.68 |
| 15 | 3+3 | % patients | 24.4 | 28.5 | 29.2 | 15.7 | 2.2 | 0.0 |
|  |  | % MTD | 4.5 | 13.1 | 15.3 | 6.7 | 0.0 | 0.0 |
| 27 | 3+3 | % patients | 16.3 | 21.0 | 28.1 | 24.6 | 9.0 | 1.0 |
|  |  | % MTD | 6.5 | 21.5 | 28.1 | 21.9 | 5.8 | 0.2 |
| 36 | 3+3 | % patients | 14.3 | 18.9 | 26.8 | 26.5 | 11.8 | 1.8 |
|  |  | % MTD | 9.4 | 23.1 | 29.8 | 23.0 | 5.2 | 0.4 |
| 48 | 3+3 | % patients | 12.8 | 17.0 | 25.9 | 28.5 | 13.8 | 2.0 |
|  |  | % MTD | 8.5 | 24.5 | 34.2 | 22.9 | 5.6 | 0.1 |
| 15 | 2+4 | % patients | 28.4 | 31.0 | 28.4 | 12.3 | 0.0 | 0.0 |
|  |  | % MTD | 2.9 | 7.3 | 9.0 | 0.0 | 0.0 | 0.0 |
| 27 | 2+4 | % patients | 17.8 | 20.9 | 26.9 | 22.7 | 9.8 | 1.9 |
|  |  | % MTD | 6.5 | 13.3 | 22.4 | 16.7 | 4.0 | 0.5 |
| 36 | 2+4 | % patients | 15.7 | 19.9 | 25.1 | 25.1 | 12.0 | 2.2 |
|  |  | % MTD | 9.4 | 23.2 | 28.0 | 17.3 | 4.4 | 0.7 |
| 48 | 2+4 | % patients | 14.2 | 18.9 | 25.0 | 25.9 | 13.6 | 2.5 |
|  |  | % MTD | 11.1 | 25.6 | 32.6 | 18.2 | 3.8 | 0.7 |
| 15 | 3+3+3 | % patients | 23.5 | 26.9 | 30.0 | 17.4 | 2.1 | 0.0 |
|  |  | % MTD | 0.2 | 1.1 | 3.5 | 5.7 | 0.0 | 0.0 |
| 27 | 3+3+3 | % patients | 13.2 | 15.8 | 21.6 | 29.9 | 17.3 | 2.2 |
|  |  | % MTD | 0.8 | 3.4 | 7.7 | 18.5 | 15.9 | 1.6 |
| 36 | 3+3+3 | % patients | 10.5 | 12.8 | 18.4 | 29.5 | 23.7 | 5.0 |
|  |  | % MTD | 2.7 | 5.8 | 11.2 | 20.5 | 21.0 | 5.4 |
| 48 | 3+3+3 | % patients | 8.7 | 11.0 | 15.8 | 28.2 | 29.0 | 7.3 |
|  |  | % MTD | 2.8 | 8.8 | 15.4 | 23.0 | 24.1 | 7.2 |
| 15 | CRM | % patients | 6.67 | 10.88 | 31.41 | 29.24 | 11.24 | 10.57 |
|  |  | % MTD | 0.0 | 6.4 | 30.1 | 39.8 | 20.6 | 3.1 |
| 27 | CRM | % patients | 3.82 | 39.71 | 31.77 | 17.88 | 4.44 | 2.38 |
|  |  | % MTD | 0.0 | 3.2 | 27.3 | 55.2 | 13.2 | 1.1 |
| 36 | CRM | % patients | 2.78 | 5.59 | 29.97 | 45.08 | 12.13 | 4.46 |
|  |  | % MTD | 0.0 | 1.0 | 24.6 | 64.1 | 10.0 | 0.3 |
| 48 | CRM | % patients | 2.08 | 5.16 | 27.95 | 49.93 | 11.46 | 3.42 |
|  |  | % MTD | 0.0 | 0.5 | 20.3 | 71.1 | 8.1 | 0.0 |

Table 4: The MTD selection and dose allocation for Scenario 4.

Dose

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  | 1 | 3 | 5 | 7 | 9 | 11 |
| n | Design | Toxicity probability : | 0.04 | 0.07 | 0.1 | 0.16 | 0.23 | 0.32 |
| 15 | 3+3 | % patients | 23.3 | 24.7 | 25.5 | 19.4 | 7.1 | 0.0 |
|  |  | % MTD | 3.3 | 6.1 | 6.9 | 6.5 | 0.0 | 0.0 |
| 27 | 3+3 | % patients | 14.7 | 15.8 | 18.0 | 20.6 | 20.2 | 10.6 |
|  |  | % MTD | 3.4 | 5.2 | 10.7 | 18.8 | 17.5 | 6.2 |
| 36 | 3+3 | % patients | 13.1 | 14.5 | 17.0 | 19.8 | 21.2 | 14.3 |
|  |  | % MTD | 2.5 | 5.7 | 11.2 | 17.7 | 14.9 | 4.7 |
| 48 | 3+3 | % patients | 12.5 | 13.4 | 16.0 | 19.1 | 22.2 | 16.8 |
|  |  | % MTD | 2.9 | 5.2 | 11.2 | 16.9 | 13.6 | 2.3 |
| 15 | 2+4 | % patients | 27.6 | 29.0 | 27.3 | 16.0 | 0.0 | 0.0 |
|  |  | % MTD | 2.0 | 3.2 | 4.6 | 0.0 | 0.0 | 0.0 |
| 27 | 2+4 | % patients | 16.4 | 17.6 | 19.6 | 20.4 | 17.1 | 9.0 |
|  |  | % MTD | 2.0 | 5.0 | 9.8 | 12.0 | 11.2 | 5.3 |
| 36 | 2+4 | % patients | 14.3 | 15.2 | 17.3 | 20.5 | 19.7 | 13.1 |
|  |  | % MTD | 1.7 | 4.7 | 10.1 | 14.7 | 13.8 | 8.2 |
| 48 | 2+4 | % patients | 13.2 | 14.3 | 16.8 | 19.7 | 21.1 | 14.9 |
|  |  | % MTD | 1.5 | 5.5 | 11.1 | 15.7 | 15.4 | 3.5 |
| 15 | 3+3+3 | % patients | 22.7 | 24.4 | 25.9 | 20.2 | 6.8 | 0.0 |
|  |  | % MTD | 0.2 | 0.3 | 0.6 | 1.5 | 0.0 | 0.0 |
| 27 | 3+3+3 | % patients | 13.4 | 14.4 | 15.9 | 19.0 | 21.9 | 15.4 |
|  |  | % MTD | 0.0 | 0.5 | 0.9 | 2.3 | 4.7 | 6.2 |
| 36 | 3+3+3 | % patients | 11.7 | 12.5 | 14.1 | 16.8 | 22.0 | 22.8 |
|  |  | % MTD | 0.0 | 0.5 | 1.4 | 3.0 | 5.1 | 4.4 |
| 48 | 3+3+3 | % patients | 11.1 | 12.1 | 13.5 | 16.1 | 21.3 | 26.0 |
|  |  | % MTD | 0.1 | 0.4 | 1.4 | 2.7 | 2.8 | 1.8 |
| 15 | CRM | % patients | 6.67 | 4.13 | 15.49 | 17.81 | 12.36 | 43.53 |
|  |  | % MTD | 0.0 | 0.5 | 5.5 | 11.1 | 23.2 | 59.7 |
| 27 | CRM | % patients | 3.70 | 2.74 | 10.00 | 14.7 | 16.80 | 52.05 |
|  |  | % MTD | 0.0 | 0.2 | 1.5 | 8.9 | 21.8 | 67.6 |
| 36 | CRM | % patients | 2.78 | 2.00 | 7.01 | 11.57 | 17.52 | 59.12 |
|  |  | % MTD | 0.0 | 0.1 | 0.6 | 3.5 | 22.9 | 72.9 |
| 48 | CRM | % patients | 2.08 | 1.41 | 5.81 | 9.8 | 19.41 | 61.49 |
|  |  | % MTD | 0.0 | 0.0 | 0.3 | 3.0 | 21.3 | 75.4 |

Table 5: The MTD selection and dose allocation for Scenario 5.

Dose

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | | | 1 | 3 | 5 | 7 | 9 | 11 |
| n | Design | Toxicity probability : | 0.05 | 0.12 | 0.240.43 |  | 0.64 | 0.81 |
| 15 | 3+3 | % patients | 25.6 | 30.4 | 30.312.5 |  | 1.3 | 0.0 |
|  |  | % MTD | 6.4 | 16.3 | 19.04.5 |  | 0.0 | 0.0 |
| 27 | 3+3 | % patients | 17.8 | 25.0 | 32.320.7 |  | 4.0 | 0.2 |
|  |  | % MTD | 10.2 | 30.4 | 32.111.7 |  | 1.1 | 0.0 |
| 36 | 3+3 | % patients | 15.7 | 23.0 | 32.123.9 |  | 5.0 | 0.3 |
|  |  | % MTD | 14.4 | 31.9 | 31.914.0 |  | 0.7 | 0.0 |
| 48 | 3+3 | % patients | 14.3 | 20.8 | 33.125.7 |  | 5.9 | 0.3 |
|  |  | % MTD | 14.0 | 34.6 | 32.813.1 |  | 0.8 | 0.0 |
| 15 | 2+4 | % patients | 28.7 | 32.4 | 28.710.2 |  | 0.0 | 0.0 |
|  |  | % MTD | 3.6 | 9.5 | 10.60.0 |  | 0.0 | 0.0 |
| 27 | 2+4 | % patients | 19.0 | 24.7 | 28.820.7 |  | 6.1 | 0.7 |
|  |  | % MTD | 8.0 | 24.5 | 22.711.1 |  | 1.6 | 0.0 |
| 36 | 2+4 | % patients | 17.0 | 23.4 | 29.922.4 |  | 6.6 | 0.7 |
|  |  | % MTD | 13.6 | 28.8 | 30.99.1 |  | 1.2 | 0.0 |
| 48 | 2+4 | % patients | 15.9 | 22.5 | 29.823.2 |  | 7.8 | 0.8 |
|  |  | % MTD | 16.3 | 34.5 | 30.89.6 |  | 1.3 | 0.1 |
| 15 | 3+3+3 | % patients | 23.4 | 28.7 | 31.915.0 |  | 1.0 | 0.0 |
|  |  | % MTD | 0.3 | 2.1 | 7.37.7 |  | 0.0 | 0.0 |
| 27 | 3+3+3 | % patients | 13.8 | 17.8 | 27.431.2 |  | 9.5 | 0.4 |
|  |  | % MTD | 2.0 | 7.0 | 13.322.9 |  | 8.4 | 0.1 |
| 36 | 3+3+3 | % patients | 11.1 | 14.3 | 23.836.3 |  | 13.5 | 1.0 |
|  |  | % MTD | 3.5 | 10.5 | 19.324.9 |  | 13.4 | 1.1 |
| 48 | 3+3+3 | % patients | 9.4 | 12.8 | 21.737.7 |  | 17.0 | 1.3 |
|  |  | % MTD | 4.5 | 15.4 | 25.423.0 |  | 13.5 | 1.6 |
| 15 | CRM | % patients | 6.67 | 16.09 | 40.8225.98 |  | 5.34 | 5.1 |
|  |  | % MTD | 0.0 | 10.5 | 52.132.8 |  | 4.2 | 0.4 |
| 27 | CRM | % patients | 3.70 | 13.78 | 45.7129.75 |  | 4.68 | 2.98 |
|  |  | % MTD | 0.0 | 7.2 | 54.237.1 |  | 1.5 | 0.0 |
| 36 | CRM | % patients | 2.78 | 11.16 | 48.8331.64 |  | 3.54 | 2.04 |
|  |  | % MTD | 0.0 | 3.5 | 59.136.4 |  | 1.0 | 0.0 |
| 48 | CRM | % patients | 2.08 | 9.49 | 51.7232.46 |  | 2.69 | 1.56 |
|  |  | % MTD | 0.0 | 2.1 | 62.535.3 |  | 0.1 | 0.0 |

Table 6: The MTD selection and dose allocation for Scenario 6.

Dose

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | | | 1 | 3 | 5 | 7 | 9 | 11 |
| n | Design | Toxicity probability : | 0.05 | 0.07 | 0.12 | 0.19 | 0.280.39 |  |
| 15 | 3+3 | % patients | 23.7 | 25.3 | 26.2 | 18.9 | 5.80.0 |  |
|  |  | % MTD | 3.5 | 7.2 | 9.8 | 7.2 | 0.00.0 |  |
| 27 | 3+3 | % patients | 14.9 | 16.3 | 19.9 | 22.2 | 19.27.5 |  |
|  |  | % MTD | 3.6 | 8.0 | 16.3 | 21.1 | 17.63.8 |  |
| 36 | 3+3 | % patients | 12.8 | 14.5 | 17.5 | 21.6 | 22.311.4 |  |
|  |  | % MTD | 3.3 | 6.9 | 17.5 | 21.6 | 16.85.6 |  |
| 48 | 3+3 | % patients | 12.0 | 13.5 | 16.6 | 21.5 | 23.712.7 |  |
|  |  | % MTD | 3.5 | 7.8 | 17.9 | 22.7 | 14.32.3 |  |
| 15 | 2+4 | % patients | 27.5 | 29.3 | 27.5 | 15.7 | 0.00.0 |  |
|  |  | % MTD | 1.7 | 4.4 | 5.6 | 0.0 | 0.00.0 |  |
| 27 | 2+4 | % patients | 16.5 | 18.1 | 20.1 | 21.2 | 16.47.6 |  |
|  |  | % MTD | 2.1 | 7.8 | 10.8 | 15.3 | 10.94.3 |  |
| 36 | 2+4 | % patients | 14.3 | 15.5 | 18.3 | 21.7 | 19.710.5 |  |
|  |  | % MTD | 3.8 | 6.4 | 14.2 | 19.1 | 15.86.4 |  |
| 48 | 2+4 | % patients | 12.9 | 14.5 | 17.9 | 21.8 | 20.912.0 |  |
|  |  | % MTD | 3.2 | 8.8 | 17.7 | 20.2 | 15.04.5 |  |
| 15 | 3+3+3 | % patients | 22.8 | 24.9 | 26.8 | 19.9 | 5.60.0 |  |
|  |  | % MTD | 0.2 | 0.3 | 1.5 | 2.1 | 0.00.0 |  |
| 27 | 3+3+3 | % patients | 13.0 | 14.5 | 16.7 | 20.8 | 22.612.5 |  |
|  |  | % MTD | 0.1 | 0.6 | 1.4 | 4.3 | 10.78.1 |  |
| 36 | 3+3+3 | % patients | 11.2 | 12.1 | 13.9 | 17.7 | 24.121.0 |  |
|  |  | % MTD | 0.1 | 0.6 | 2.9 | 6.6 | 9.88.7 |  |
| 48 | 3+3+3 | % patients | 9.8 | 10.9 | 13.1 | 16.0 | 24.126.1 |  |
|  |  | % MTD | 0.2 | 1.6 | 3.1 | 5.7 | 7.34.5 |  |
| 15 | CRM | % patients | 6.67 | 5.83 | 17.65 | 19.96 | 13.9235.97 |  |
|  |  | % MTD | 0.0 | 1.6 | 6.9 | 18.1 | 29.344.1 |  |
| 27 | CRM | % patients | 3.70 | 3.3 | 12.56 | 19.94 | 21.638.9 |  |
|  |  | % MTD | 0.0 | 0.9 | 3.6 | 16.6 | 36.842.1 |  |
| 36 | CRM | % patients | 2.78 | 2.74 | 10.52 | 19.08 | 27.5337.35 |  |
|  |  | % MTD | 0.0 | 0.2 | 1.8 | 14.3 | 44.639.1 |  |
| 48 | CRM | % patients | 2.08 | 1.96 | 7.11 | 16.79 | 32.9739.09 |  |
|  |  | % MTD | 0.0 | 0.1 | 0.8 | 9.2 | 49.540.4 |  |

References

1. Babb, J., A. Rogatko, and S. Zacks (1998). Cancer phase I clinical trials: Efficient dose escalation with overdose control. Statistics in Medicine 17 (10), 1103–1120.
2. Boonstra, P. S., J. Shen, J. M. Taylor, T. M. Braun, K. A. Griffith, S. Daignault,
3. G. P. Kalemkerian, T. S. Lawrence, and M. J. Schipper (2015). A statistical evaluation of dose expansion cohorts in phase I clinical trials. Journal of the National Cancer Institute 107 (3), dju429.
4. Chiuzan, C., E. Garrett-Mayer, and S. D. Yeatts (2015). A likelihood-based approach for computing the operating characteristics of the 3+ 3 phase I clinical trial design with extensions to other A+ B designs. Clinical Trials 12 (1), 24– 33.
5. Collins, J. M., C. K. Grieshaber, and B. A. Chabner (1990). Pharmacologically guided phase I clinical trials based upon preclinical drug development. Journal of the National Cancer Institute 82 (16), 1321–1326.
6. Ji, Y. and S.-J. Wang (2013). Modified toxicity probability interval design: A safer and more reliable method than the 3+ 3 design for practical phase I trials. Journal of Clinical Oncology 31 (14), 1785–1791.
7. Kairalla, J. A., C. S. Coffey, M. A. Thomann, and K. E. Muller (2012). Adaptive trial designs: A review of barriers and opportunities. Trials 13 (1), 145.
8. Le Tourneau, C., J. J. Lee, and L. L. Siu (2009). Dose escalation methods in phase I cancer clinical trials. Journal of the National Cancer Institute 101 (10), 708–720.
9. Leung, D. H.-Y. and Y.-G. Wang (2001). Isotonic designs for phase I trials.Controlled Clinical Trials 22 (2), 126–138.
10. Liu, J. and D. K. Dey (2015). A type of sample size planning for mean comparison in clinical trials. Journal of Data Science 13 (1), 115–125.
11. O’Quigley, J., M. Pepe, and L. Fisher (1990). Continual reassessment method: A practical design for phase I clinical trials in cancer. Biometrics 46 (1), 33–48.
12. O’Quigley, J. and L. Z. Shen (1996). Continual reassessment method: A likelihood approach. Biometrics 52 (2), 673–684.
13. Simon, R., L. Rubinstein, S. G. Arbuck, M. C. Christian, B. Freidlin, and J. Collins (1997). Accelerated titration designs for phase I clinical trials in oncology. Journal of the National Cancer Institute 89 (15), 1138–1147.
14. Singh, K., A. Bartolucci, and S. Bae (2010). The Bayesian multiple logistic random effects model for analysis of clinical trial data. Journal of Data Sci- ence 8 (3), 495–504.
15. Storer, B. E. (1989). Design and analysis of phase I clinical trials. Biomet- rics 45 (3), 925–937.

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