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Bayesian optimal interval design for phase I oncology clinical trials

Bryan M. Fellman
MD Anderson Cancer Center
Houston, TX
bmfellman@mdanderson.org

Ying Yuan
MD Anderson Cancer Center
Houston, TX
yyuan@mdanderson.org

Abstract. The Bayesian optimal interval (BOIN) design is a novel phase I trial design for finding the maximum tolerated dose (MTD). With the BOIN design, phase I trials are conducted as a sequence of decision-making steps for assigning an appropriate dose for each enrolled patient. The design optimizes the assignment of doses to patients by minimizing incorrect decisions of dose escalation or de-escalation; that is, it decreases the chance of erroneously escalating or de-escalating the dose when the current dose is higher or lower than the MTD. This feature of the BOIN design strongly ensures adherence to ethical standards. The most prominent advantage of the BOIN design is that it simultaneously achieves design simplicity and superior performance in comparison with similar methods. The BOIN design can be implemented in a simple way that is similar to the $3 + 3$ design, but it yields substantially better operating characteristics. Compared with the well-known continual reassessment method, the BOIN design yields average performance when selecting the MTD, but it has a substantially lower risk of assigning patients to subtherapeutic or overly toxic doses. In this article, we present a command (`optinterval`) for implementing the BOIN design in a phase I clinical trial setting.

Keywords: st0372, optinterval, Bayesian optimal interval, phase I clinical trial design, maximum tolerated dose, operating characteristic

1 Introduction

Many phase I trial designs have been proposed to identify the maximum tolerated dose (MTD) of a new drug. These methods can be classified into algorithm-based and model-based approaches. Algorithm-based designs do not assume any dose-toxicity curve, except that toxicity monotonically increases with the dose. This family of designs conducts dose escalation and de-escalation strictly according to the prespecified algorithm. The most commonly used algorithm-based method is the $3 + 3$ design (Storer 1989). Other algorithm-based methods include the accelerated titration designs (Simon et al. 1997), the random walk rule (Durham, Flournoy, and Rosenberger 1997) and its improved up-and-down design (Leung and Wang 2001), and the biased coin design (Stylianou and Flournoy 2002). Algorithm-based methods are robust because they do not rely on any parametric model structures, and they are easy to implement by following a set of prespecified rules. However, these designs, particularly the $3 + 3$ design, have been criticized for poor operating characteristics.

Model-based dose-finding designs assume a parametric dose-toxicity model. During the trial, the model parameter is continuously updated using all the observed data, and dose-escalation decisions are made using the estimated toxicity probabilities from the dose-toxicity model. The best-known example of model-based designs is the continual reassessment method (CRM) (O'Quigley, Pepe, and Fisher 1990). By modeling all the observed data, the CRM has been shown to be superior to the algorithm-based $3 + 3$ design. However, this model must be fit repeatedly, so it is more complicated to implement in practice than the BOIN design.

The Bayesian optimal interval (BOIN) design combines the advantages of algorithm-based designs (that is, simplicity and robustness) and model-based designs (that is, superior performance). It uses a Bayesian model for deriving the optimal decision rule for dose escalation or de-escalation, while the implementation of the design takes a form of algorithm-based designs. The BOIN design can be implemented in a simple way similar to the $3 + 3$ design, but it yields superior operating characteristics comparable with (or better than) that of the CRM. The design is optimal in that it minimizes the chance of assigning patients to subtherapeutic or overly toxic doses, which is a top priority and concern among clinicians seeking to effectively treat patients.

The idea behind the BOIN design is straightforward. Phase I trials are conducted as a sequence of decision-making steps of dose assignment for patients enrolled in the trial. At each moment of decision making, using the observed data, we do one of three things: escalate, de-escalate, or retain the current dose. Under the standard assumption that efficacy monotonically increases with toxicity (for cytotoxic agents), an ideal trial design would escalate the dose when the current dose is below the MTD to avoid treating a patient at a subtherapeutic dose level; de-escalate the dose when the current dose is above the MTD to avoid exposing a patient to an overly toxic dose; and retain the same dose level when the current dose is equal (or close) to the MTD. However, such an ideal design is not available in practice because we do not know whether the current dose is actually below, above, or equal (or close) to the MTD, and we must infer that information and make decisions using the data collected from patients who have been enrolled and treated in the trial. Because of the randomness of the observed data and small-sample sizes of phase I trials, we often make incorrect decisions for dose assignment; for example, we may erroneously escalate (or de-escalate) the dose when it is actually higher (or lower) than the MTD, which results in overly aggressive (or conservative) dose assignments and treating excessive numbers of patients at dose levels above (or below) the MTD. From a practical and ethical viewpoint, it is highly desirable to minimize these decision errors so that the design behaves as closely as possible to the ideal (error-free) design. The BOIN design is proposed to achieve this goal.

The BOIN design possesses sound theoretical properties. It is long-memory coherent in that the probability of dose escalation (or de-escalation) is zero when the observed toxicity rate, $\widehat{p_j}$, at the current dose is higher (or lower) than the target toxicity rate, ϕ_j. Conversely, the probability of de-escalation is zero when $\widehat{p_j} < \phi_j$. The BOIN design has a convergence property similar to that of the CRM, and it converges almost entirely at a $\sqrt{n}$ rate to exclusive allocations of the target dose. The numerical study evaluating the designs performance shows that the BOIN design has superior operating characteristics

that are comparable with or better than those of the CRM but that are much easier to implement.

In this design, dose transition is defined by the relative location of the observed toxicity rate (that is, the number of patients who experienced toxicity divided by the total number of patients treated) at the current dose with respect to a prespecified toxicity tolerance interval. If the observed toxicity rate is located within the interval, we retain the current dose; if the observed toxicity rate is greater than the upper boundary of the interval, we de-escalate the dose; and if the observed toxicity rate is smaller than the lower boundary of the interval, we escalate the dose. To use the BOIN design, we need to specify only the interval (or dose escalation or de-escalation) boundaries at the trial design phase, because they are the only design parameters that control dose escalation or de-escalation. When clinicians conduct the trial, they need no additional software and can simply count the number of patients who experience toxicity and compare the observed toxicity rate with the prespecified dose escalation or de-escalation boundaries to determine dose assignment until the trial is completed.

2 Methods

The complete description of the BOIN design is detailed in Liu and Yuan (2015). Below is a brief overview of the design.

2.1 Interval design

Assume we have J prespecified doses to be examined, and denote ϕ as the target toxicity rate. Then, the interval design can be described as follows:

1. Patients in the first cohort are treated at the lowest dose level.
2. At the current dose level j, assume that a total of n_j patients have been treated and m_j of them have experienced a toxicity. Let $\widehat{p}_j = m_j/n_j$ denote the observed toxicity rate at dose level j, and let $\lambda_{1j}(n_j, \phi)$ and $\lambda_{2j}(n_j, \phi)$ denote the prespecified lower and upper boundaries of the interval, respectively, with $0 \leq \lambda_{1j}(n_j, \phi) \leq \lambda_{2j}(n_j, \phi) \leq 1$. The next cohort dose assignment will be decided by the following steps:
   a. if $\widehat{p}_j \leq \lambda_{1j}(n_j, \phi)$, escalate the dose level to $j + 1$;
   b. if $\widehat{p}_j \geq \lambda_{2j}(n_j, \phi)$, de-escalate the dose level to $j - 1$;
   c. otherwise, $\lambda_{1j}(n_j, \phi) < \widehat{p}_j < \lambda_{2j}(n_j, \phi)$.
3. Continue step 2 until the maximum sample size is reached.

2.2 Local BOIN design

The notations $\lambda_{1j}(n_j, \phi)$ and $\lambda_{2j}(n_j, \phi)$ will be simplified to λ_{1j} and λ_{2j}, respectively. The local BOIN design selects λ_{1j} and λ_{2j} to minimize incorrect decision of dose escalation and de-escalation in which the optimization is based upon three point (or local) hypotheses. To minimize incorrect decisions on dose assignment, we will define correct and incorrect decisions as follows. Let p_j be the true toxicity probability of dose level j for $j = 1, \ldots, J$. We then define the three point hypotheses as

$$\begin{aligned} H_{0j}: &\quad p_j = \phi \\ H_{1j}: &\quad p_j = \phi_1 \\ H_{2j}: &\quad p_j = \phi_2 \end{aligned}$$

where ϕ_1 denotes the highest toxicity probability deemed subtherapeutic, suggesting that dose escalation is required, and ϕ_2 denotes the lowest toxicity probability deemed overly toxic, suggesting that dose de-escalation is required. Hence, H_{0j} indicates that the current dose is the MTD and should be retained for the next cohort of patients, H_{1j} indicates that the current dose is below the MTD and dose escalation should occur, and H_{2j} indicates that the current dose is above the MTD and dose de-escalation should occur. That is, the correct decisions under H_0, H_1, and H_2 are retainment, escalation, and de-escalation (each based on the current dose level), denoted as R, E, and D, respectively. Correspondingly, the incorrect decisions under H_0, H_1, and H_2 are $\overline{R}$, $\overline{E}$, and $\overline{D}$, respectively, where $\overline{R}$ denotes the decisions complementary to R (that is, $\overline{R}$ includes E and D), and $\overline{D}$ and $\overline{R}$ denote the decisions complementary to D and R.

Under the Bayesian paradigm, we assign each of the hypotheses a prior probability of being true, denoted as $\pi_{kj} = \Pr(H_{kj}), k = 0, 1, 2$. Then, under the proposed design, the probability of making an incorrect decision (the decision error rate), denoted as $\alpha(\lambda_{1j}, \lambda_{2j})$, at each of the dose assignments is given by

$$\alpha(\lambda_{1j}, \lambda_{2j}) = \Pr(H_{0j}) \Pr\left(\overline{R} \,|\, H_{0j}\right) + \Pr\left(H_{1j}\right) \Pr\left(\overline{E} \,|\, H_{1j}\right) + \Pr\left(H_{2j}\right) \Pr\left(\overline{D} \,|\, H_{2j}\right)$$

Assuming equal prior probabilities to the three hypotheses (that is, $\pi_{0j} = \pi_{1j} = \pi_{2j} = 1/3$), we can show that the decision error rate is minimized when

$$\lambda_{1j} = \frac{\log\left(\dfrac{1-\phi_1}{1-\phi}\right)}{\log\left\{\dfrac{\phi(1-\phi_1)}{\phi_1(1-\phi)}\right\}} \quad \text{and} \quad \lambda_{2j} = \frac{\log\left(\dfrac{1-\phi}{1-\phi_2}\right)}{\log\left\{\dfrac{\phi_2(1-\phi)}{\phi(1-\phi_2)}\right\}}$$

2.3 Global BOIN design

The global BOIN design accounts for all possible values of p_j by specifying three composite hypotheses. Values of λ_{1j} and λ_{2j} are chosen to minimize the average decision error over the whole support of $p_j \in (0, 1)$. Specifically, the three composite hypotheses are

$$\begin{aligned} H_{0j}: &\quad \phi_1 < p_j < \phi_2 \\ H_{1j}: &\quad 0 \le p_j \le \phi_1 \\ H_{2j}: &\quad \phi_2 \le p_j \le 1 \end{aligned}$$

where H_{0j} indicates that dose level j is close to the MTD and that the dose should be retained, H_{1j} indicates that dose level j is below the MTD and that the dose should be escalated, and H_{2j} indicates that the dose level is too toxic and that the dose should be de-escalated. Let $f(p_j \mid H_{kj})$ denote the prior distribution of p_j under H_{kj} for $k = 0, 1, 2$. The global decision error rate is given by

$$\begin{aligned} \alpha_g(\lambda_{1j}, \lambda_{2j}) = \Pr(H_{0j}) &\int f(p_j \mid H_{0j}) \Pr\left(\overline{R} | p_j, H_{0j}\right) \, \mathrm{d}p_j \\ + \Pr(H_{1j}) &\int f(p_j \mid H_{1j}) \Pr\left(\overline{E} \mid p_j, H_{1j}\right) \, \mathrm{d}p_j \\ + \Pr(H_{2j}) &\int f(p_j \mid H_{2j}) \Pr\left(\overline{D} \mid p_j, H_{2j}\right) \, \mathrm{d}p_j \end{aligned}$$

Unlike that of the local BOIN design, the minimization of the global decision error, $\alpha_g(\lambda_{1j}, \lambda_{2j})$, does not yield closed forms of λ_{1j} and λ_{2j}, and it requires numerical search. Additionally, numerical studies show that the local BOIN design has better operating characteristics than the global BOIN design. Therefore, we recommend the local BOIN design for general use in practice.

2.4 Stopping rule for safety

Because BOIN designs use only the toxicity information at the current dose level to determine escalation rules, the dose assignment alternates between two adjacent doses when one of the doses is much lower than the MTD and the other is much higher than the MTD. Therefore, we implemented the following rule to ensure patient safety, and to avoid assigning too many patients to an overly toxic dose: if $\Pr(p_j > \phi \mid t_j, n_j) > \pi_*$ and $n_j \ge 3$, then dose levels j and higher are eliminated from the trial, where $\Pr(p_j > \phi \mid t_j, n_j)$ can be evaluated using a beta-binomial model with a prior for $p_j \sim \beta(1, 1)$. This means that doses will be eliminated if the posterior probability that the current dose's toxicity rate is higher than the target toxicity rate is greater than some upper bound π_*. We also allow a different π_* to be used for dose one explicitly. We recommend that the cutoff, π_*, be lower than the cutoff used for doses greater than the first dose. This is done for greater safety when the first dose's toxicity rate is higher than the target rate.

3 The optinterval command

3.1 Syntax

```
optinterval, target(#) ncohort(#) [getboundary selectmtd oc design(#)
  cohort(#) saf(#) tox(#) cut(#) cut1(#) npts(numlist) ntox(numlist)
  startdose(#) truep(numlist) ntrials(#)]
```

3.2 Options

`target(#)` specifies the target toxicity rate. `target()` is required and must be greater than 0.05 and less than or equal to 0.60.

`ncohort(#)` specifies the total number of cohorts to be enrolled. `ncohort()` is required.

`getboundary` specifies that the dose escalation rules for a proposed design be calculated.

`selectmtd` specifies finding the MTD at the end of a trial.

`oc` specifies that the operating characteristics for a proposed design be calculated.

`design(#)`, with `1`, specifies the local optimal design and, with `2`, specifies the global optimal design. The default is `design(1)`.

`cohort(#)` specifies the cohort size. The default is `cohort(1)`.

`saf(#)` specifies the highest toxicity probability that is deemed subtherapeutic (that is, below the MTD) such that dose escalation is required. The default is `saf(0.6 ×` `target(#))`.

`tox(#)` specifies the lowest toxicity probability that is deemed overly toxic (that is, above the MTD) such that dose de-escalation is required. The default is `tox(1.4 ×` `target(#))`.

`cut(#)` specifies the cutoff to eliminate the overly toxic doses for safety monitoring of doses greater than the first dose. The default is `cut(0.95)`.

`cut1(#)` specifies the cutoff to eliminate the overly toxic dose for safety monitoring of only the first dose. The default is `cut1(0.95)`.

`npts(`*numlist*`)` specifies the number of patients treated at each dose at the end of the trial. `npts()` is required when `selectmtd` is specified.

`ntox(`*numlist*`)` specifies the number of toxicities at each dose at the end of the trial. `ntox()` is required when `selectmtd` is specified.

`startdose(#)` specifies the starting dose for the trial. The default is `startdose(1)`.

`truep(`*numlist*`)` specifies the true toxicity probabilities for each dose. `truep()` is required when `oc` is specified.

`ntrials(#)` specifies the number of trials to simulate when calculating operating characteristics. The default is `ntrials(10000)`.

4 Examples

Suppose we have a proposed new therapeutic treatment to improve survival in a specific cancer population. We must conduct a phase I clinical trial to find the MTD of the new treatment. We will conduct our trial using the BOIN design. The trial will enroll patients in cohorts of size 3 and will enroll a total of 10 cohorts. The toxicity rate of the new treatment is targeted to be 0.30. We have selected the elimination cutoff boundary, π_*, for dose 1 to be 0.85. This is 0.10 lower than the cutoff for doses greater than dose 1. This is done to ensure that if dose 1 is overly toxic, we will eliminate it with higher probability.

4.1 Escalation or de-escalation boundaries

To conduct our trial, we will need the predefined escalation and de-escalation boundaries. We can obtain these by using `optinterval` as follows:

```
. optinterval, getboundary target(0.3) ncohort(10) cohort(3) cut1(0.85)

Escalate dose if the observed toxicity rate at the current dose <= .23649069
Deescalate dose if the observed toxicity rate at the current dose >= .35851946

This is equivalent to the following decision boundaries
```

N	Escalate (if # DLT <=)	Deescalate (if # DLT >=)	Eliminate Dose 1 (if # DLT >=)	Eliminate Doses > 1 (if # DLT >=)
3	0	2	2	3
6	1	3	3	4
9	2	4	5	5
12	2	5	6	7
15	3	6	7	8
18	4	7	8	9
21	4	8	9	10
24	5	9	10	11
27	6	10	11	12
30	7	11	12	14

For example, if 0 toxicities were observed in the first cohort of 3 patients, we would escalate to dose level 2. If 6 patients were treated at a particular dose and 1 or fewer toxicities were observed, we would escalate the dose. On the other hand, if 3 or more toxicities were observed, we would de-escalate. If the 6 patients were treated at dose level 1 and 3 toxicities or more were observed, dose 1 would be eliminated. If it were a dose larger than dose 1, then 4 toxicities or more would be needed to eliminate that particular dose. In this example, if we did not want to limit ourselves to a constant cohort size, we would set `ncohort(30)` and `cohort(1)` to list all possible escalation

rules. This would allow us to make our decision at any time in the trial for any given number of patients treated at a current dose.

4.2 Operating characteristics

It is often useful to obtain the operating characteristics of the design to ensure that the trial will be conducted as planned for a particular set of hypothetical toxicity rates at each dose level. First, we must construct a set of representative dose-toxicity scenarios that may be encountered in the trial. These scenarios should have different locations of the MTD and different shapes of the dose-toxicity curve. Second, through simulation, we can evaluate the probability of correct selection of the true MTD and the number of patients assigned to each dose. Good operating characteristics indicate that the design has good selection percentage of the MTD and that it assigns a large number of patients to the MTD across all scenarios. Using the same design as in section 4.1, we can obtain the operating characteristics for different dose-toxicity scenarios as follows:

```
. set seed 1234
. optinterval, oc target(0.30) ncohort(10) cohort(3)
> truep(0.40 0.50 0.55 0.60 0.70) cut1(0.85)
```

Dose	1	2	3	4	5
Pr(Toxicity)	0.40	0.50	0.55	0.60	0.70
% Selected	23.93	4.46	0.59	0.03	0.03
Avg Toxicity	4.42	1.56	0.25	0.03	0.00
Avg Patients	11.01	3.10	0.45	0.05	0.00

```
Avg Patients = 14.61
Avg Toxicities = 6.26

% Dose 1 overly toxic = 70.96

. optinterval, oc target(0.30) ncohort(10) cohort(3)
> truep(0.30 0.40 0.45 0.50 0.60) cut1(0.85)
```

Dose	1	2	3	4	5
Pr(Toxicity)	0.30	0.40	0.45	0.50	0.60
% Selected	34.74	18.54	5.53	1.32	0.13
Avg Toxicity	3.62	2.58	0.83	0.21	0.04
Avg Patients	12.01	6.49	1.88	0.41	0.07

```
Avg Patients = 20.85
Avg Toxicities = 7.28

% Dose 1 overly toxic = 39.74
```

```
. optinterval, oc target(0.30) ncohort(10) cohort(3)
> truep(0.05 0.15 0.30 0.45 0.60) cut1(0.85)
```

Dose	1	2	3	4	5
Pr(Toxicity)	0.05	0.15	0.30	0.45	0.60
% Selected	1.19	23.48	53.91	19.00	1.61
Avg Toxicity	0.20	1.37	3.33	2.14	0.49
Avg Patients	4.10	9.10	11.04	4.73	0.82

```
Avg Patients = 29.78
Avg Toxicities = 7.52

% Dose 1 overly toxic = .81

. optinterval, oc target(0.30) ncohort(10) cohort(3)
> truep(0.05 0.15 0.20 0.25 0.30) cut1(0.85)
```

Dose	1	2	3	4	5
Pr(Toxicity)	0.05	0.15	0.20	0.25	0.30
% Selected	1.20	9.22	20.02	28.81	39.88
Avg Toxicity	0.21	1.02	1.42	1.52	1.67
Avg Patients	4.16	6.68	7.19	6.15	5.59

```
Avg Patients = 29.77
Avg Toxicities = 5.84

% Dose 1 overly toxic = .87
```

In the first scenario, the first dose is higher than the target toxicity rate; in the second scenario, the first dose is the target toxicity rate; in the third scenario, the target toxicity rate lies in the middle of the dose-toxicity curve; and in the fourth scenario, the last dose is the target toxicity rate. Notice that the target toxicity rate, 0.30, is selected the majority of the time, indicating that the characteristics of this design perform well under the given hypothesized toxicity rates.

4.3 Selecting MTD

When the trial is completed, we can select the MTD by using the observed data. We select the MTD by finding the dose that has an isotonic estimate of toxicity rate closest to the target rate. We can do this by using `optinterval` as follows:

```
. optinterval, selectmtd target(0.30) npts(3 6 12 3 0 0) ntox(0 1 3 2 0 0)
> cut1(0.85)

The MTD is dose level 3
```

Dose	Posterior DLT Estimate	95% Credible Interval	Prob DLT > .3
1	0.016	0.000 - 0.196	0.013
2	0.172	0.006 - 0.527	0.177
3	0.252	0.062 - 0.519	0.318
4	0.661	0.160 - 0.985	0.910
5	- - -	- - - - - - -	- - -
6	- - -	- - - - - - -	- - -

For this combination of toxicities and patients at each dose, the MTD for this drug would be dose 3. A table of posterior dose-limiting toxicity estimates is presented with a corresponding 95% credible interval along with the probability that the dose's toxicity rate is greater than the target rate.

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About the authors

Bryan Fellman is a research statistical analyst in the Department of Biostatistics at the University of Texas MD Anderson Cancer Center.

Ying Yuan is an associate professor in the Department of Biostatistics at the University of Texas MD Anderson Cancer Center. His research interests include Bayesian adaptive clinical trial design and statistical analysis of missing data. Yuan has published numerous research papers on Bayesian adaptive clinical trial design, including phase I, II, I/II, adaptive randomization, and drug combination trials.