**Template for Protocol Preparation**

Consider a phase I trial with 5 dose levels, for which we assume a maximum sample size of 30 patients and a target toxicity rate of 30%. **A template for using the BOIN design is described as follows:**

We will employ the Bayesian optimal interval (BOIN) design (Liu and Yuan, 2015) to find the MTD. The BOIN design is a novel Bayesian dose-finding method that optimizes patient ethics by minimizing the chance of exposing patients to sub-therapeutic and overly toxic doses. The BOIN design yields an average performance comparable to that of the continual reassessment method (CRM) in terms of selecting the MTD, but has a lower risk of assigning patients to sub-therapeutic or overly toxic doses (i.e., better patient ethics).

The target toxicity rate for the MTD is 0.3 and the maximum sample size is 30. We will enroll and treat patients in cohorts of size 3. The trial design is described as follows:

1. Patients in the first cohort are treated at the lowest [or a prespecified] dose level.
2. To assign a dose to the next cohort of patients, we conduct dose escalation/de-escalation according to the rule displayed in Table 1.

Table 1. Dose escalation/de-escalation rule for the BOIN design.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | The number of patients treated **at the current dose** | | | | | | | | | |
| Action | 3 | 6 | 9 | 12 | 15 | 18 | 21 | 24 | 27 | 30 |
| Escalate if # of patients  who experienced DLT <= | 0 | 1 | 2 | 2 | 3 | 4 | 4 | 5 | 6 | 7 |
| De-escalate if # of patients  who experienced DLT >= | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
| Eliminate if # of patients  who experienced DLTs >= | 3 | 4 | 5 | 7 | 8 | 9 | 10 | 11 | 12 | 14 |

When using Table 1, please note the following

1. “Eliminate” means that we eliminate the current and higher doses from the trial to prevent treating any future patients at these doses because they are overly toxic.
2. When we eliminate a dose, we automatically de-escalate the dose to the next lower level. When the lowest dose is eliminated, we stop the trial for safety. In this case, no dose should be selected as the MTD.
3. If none of the actions (i.e., escalation, de-escalation or elimination) is triggered, we treat the new patients at the current dose.
4. If the current dose is the lowest dose and the rule indicates dose de-escalation, we will treat the new patients at the lowest dose unless the number of DLTs reaches the elimination boundary, at which point we will terminate the trial for safety.
5. If the current dose is the highest dose and the rule indicates dose escalation, we will treat the new patients at the highest dose.
6. Repeat step 2 until the maximum sample size of 30 is reached or the trial is stopped.

After the trial is completed, we select the MTD based on isotonic regression as specified in Liu and Yuan (2015). Specifically, we select as the MTD the dose for which the isotonic estimate of the toxicity rate is closest to the target toxicity rate. If there are ties, we select the higher dose level when the isotonic estimate is lower than the target toxicity rate; and we select the lower dose level when the isotonic estimate is greater than the target toxicity rate.

[In case there is cohort expansion after identifying the MTD] Once we determine the MTD, an additional 15 patients will be enrolled for additional experience with safety and efficacy. We will use the elimination boundaries in Table 1 for toxicity monitoring.

**Operating characteristics**

Table 2 shows the operating characteristics of the proposed design for this trial with 5 scenarios defined by different DLT rates for 5 doses. These operating characteristics are based on 1000 simulations of the trial. The operating characteristics show that the design selects the true MTD with high probabilities and allocates more patients to the dose levels with the DLT rate closest to the target of 0.3.

Table 3. Operating Characteristics of the BOIN design

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | Dose level | | | | | Number of pts | % early stopping |
|  | 1 | 2 | 3 | 4 | 5 |  |  |
| True DLT rate | 0.05 | 0.10 | **0.30** | 0.45 | 0.60 |  |  |
| Selection % | 0.2 | 17.3 | **60.2** | 20.9 | 1.4 | 30.0 | 0.0 |
| # pts treated | 3.7 | 8.1 | **12.1** | 5.3 | 0.8 |  |  |
| True DLT rate | 0.12 | **0.30** | 0.46 | 0.60 | 0.70 |  |  |
| Selection % | 19.2 | **60.9** | 17.8 | 1.6 | 0 | 29.9 | 0.5 |
| # pts treated | 9.1 | **14.0** | 5.9 | 0.9 | 0.1 |  |  |
| True DLT rate | **0.26** | 0.50 | 0.65 | 0.75 | 0.80 |  |  |
| Selection % | **74.7** | 14.3 | 0.2 | 0 | 0 | 27.8 | 10.8 |
| # pts treated | **19.4** | 7.5 | 0.8 | 0 | 0 |  |  |
| True DLT rate | 0.05 | 0.10 | 0.16 | **0.30** | 0.50 |  |  |
| Selection % | 0.2 | 2.1 | 26.2 | **56.1** | 15.4 | 30.0 | 0.0 |
| # pts treated | 3.7 | 5.0 | 8.1 | **9.3** | 3.9 |  |  |
| True DLT rate | 0.02 | 0.03 | 0.05 | 0.12 | **0.30** |  |  |
| Selection % | 0 | 0 | 0.4 | 21.3 | **78.3** | 30.0 | 0.0 |
| # pts treated | 3.2 | 3.3 | 3.8 | 7.2 | **12.5** |  |  |
| True DLT rate | 0.5 | 0.65 | 0.75 | 0.80 | 0.90 |  |  |
| Selection % | 17.9 | 0.0 | 0 | 0 | 0 | 14.6 | 82.1 |
| # pts treated | 13.4 | 1.1 | 0 | 0 | 0 |  |  |

**Remarks:**

1. If there is substantial prior knowledge that the first dose might be overly toxic, we can turn on the extra safe option by setting “extrasafe=T” in functions get.boundary() and get.oc(). The extra safety option improves safety when the first dose is overly toxic, but as a tradeoff, it slightly decreases the rate of selecting the MTD when the true MTD is dose level 1 or 2. When the extra safe option is used, please add the following statement at the end of Step 2 on page 2.

To take extra precaution for patient safety, we will also impose the following stopping rule when we are treating patients at the lowest dose level: Stop the trial if (1) the number of patients treated at the lowest dose ≥ 3 AND (2) Pr(the toxicity rate of the lowest dose > 0.3|data) > 0.9, which corresponds to the following stopping boundaries:

Table 2. Stopping boundaries for the lowest dose level

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | The number of patients treated at **the lowest dose level** | | | | | | | | | |
| Action | 3 | 6 | 9 | 12 | 15 | 18 | 21 | 24 | 27 | 30 |
| Stop the trial if # of DLTs >= | 2 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 12 | 13 |

2. In some applications, investigators may prefer to stop the trial early and select the MTD when a certain number of patients (say 12) have been treated at one dose. This can be done by setting n.earlystop=12 in function get.boundary(). This early stopping rule saves the sample size, particularly when the MTD is at a low dose level, but as a tradeoff, it may affect the rate of selecting the MTD and decrease the rate of stopping for safety if the first dose is overly toxic. If we use this approach, we only need to list the boundaries up to n.earlystop (=12) patients in Table 1, and add the following statement after Table 1: “During the trial conduct, if the number of patients treated at the current dose reaches 12, we will stop the trial early and select the MTD based on the observed data.”

Reference: Liu S. and Yuan, Y. (2015). Bayesian Optimal Interval Designs for Phase I Clinical Trials, *Journal of the Royal Statistical Society: Series C*, 64, 507-523.