U-Design
Version 1.4

Singe-Agent Dose-Finding Designs with Toxicity Endpoint and Rolling Enrollment

Your trial designs anywhere, anytime

November 2, 2020

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1. Single-Agent Dose-Finding Designs with Toxicity Endpoint and Rolling Enrollment

1.1 Introduction

Phase I oncology dose-finding trials assign cancer patients to ascending doses of a new investigational drug (or drug combinations) and adaptively decide the dose level of newly enrolled patients based on observed binary dose-limiting toxicity (DLT) outcomes. The goal is to determine the maximum tolerated dose (MTD) of the drug(s), defined as the highest dose that has a toxicity probability less than or close to a prespecified target rate $p_T$. Most popular statistical designs, such as the 3+3 (Storer, 1989), CRM (O’Quigley et al., 1990), mTPI-2 (Guo et al., 2017), and i3+3 (Liu et al., 2020) designs described in the Single-Agent Dose-Finding Designs with Toxicity Endpoint and Rolling Enrollment module, typically enroll patients in cohorts and apply sequential decisions that determine the dose level for each cohort based on observed toxicity data. Accrual is suspended after enrollment of each cohort of patients until all the patients in the current cohort have observed outcomes, with or without DLTs. This type of cohort-based designs can be inefficient, especially if the trial needs to be frequently suspended. See Skolnik et al. (2008) and Doussau et al. (2016) for discussion. For example, subsequent patients can be turned away during trial suspension, resulting in waste of precious patient resource. In addition, trial duration is prolonged due to between-cohort suspension.

To shorten the study conduct timeline of phase I trials and reduce the number of accrual suspensions, this module describe some rolling-based designs, which allows concurrent patient enrollment that is faster than cohort-base enrollment, including the rolling six (Skolnik et al., 2008) and R-TPI designs (Guo et al., 2019). Besides, mTPI-2 (Guo et al., 2017) and 3+3 (Storer, 1989) designs, with the ethics constraint of “decision-in-advance” applicable to the real-life trials, are also included for comparison. See more technical details in Section 1.3.
Besides the operating characteristics in terms of the safety and reliability reported in the Single-Agent Dose-Finding Designs with Toxicity Endpoint and Rolling Enrollment module, this module enables users to compare the trial duration based on real-life settings, which are characterized as three user-input parameters, the mean inter-patient arrival time, the maximum DLT follow-up period, and the probability of inevaluability (such as drop off) of enrollment patients. The procedure of simulating patients enrollment and evaluation is described in details in Section 1.3.1.

Hereinafter, the terms “Enrollment” and “Accrual” are used interchangeably.
1.2 User Interface and Tutorial

1.2.1 Overview

Entering the Single-Agent Dose-Finding Designs with Toxicity Endpoint and Rolling Enrollment page, users will see four main tabs: Simulation Setup, Simulation Results, Decision Table and MTD Estimation. The first two tabs allow users to conduct simulations and visualize/download simulation results, and the next two tabs allow users to generate decision tables and estimate the MTD, respectively. In the Simulation Setup tab, there are four steps (Figure 1.1): 1) Set enrollment parameters, 2) Set trial parameters, 3) Select designs, and 4) Generate scenarios. Users need to complete the steps 1-4 to set up simulations for a single design or multiple designs. Upon completing steps 1-4, users click the “Launch Simulation” button at the bottom of the page. Users may also click the “Reset” button next to Launch Simulation to clear all settings. After the simulation is launched, the results of simulations will be displayed in the Simulation Results tab. The simulation process can be monitored in real time at the top of the Simulation Results tab. Detailed steps of using this module are elaborated next in §1.2.2-§1.2.5.
Figure 1.1: Simulation setup in the **Single-Agent Dose-Finding Designs with Toxicity Endpoint and Rolling Enrollment**
1.2. User Interface and Tutorial

1.2.2. Simulation Setup

In the Single-Agent Dose-Finding Designs with Toxicity Endpoint and Rolling Enrollment module, U-Design provides four designs, mTPI-2, 3+3, Rolling 6 and R-TPI, for simulation. Users can choose up to design configurations for simultaneous comparison in the Simulation Setup tab each time. A design configuration means a design such as R-TPI, along with the designs settings, such as sample size. Request to allow more than four design configurations by emailing admin@laiyaconsulting.com.

1.2.2.1 Step 1: Set enrollment parameters

Specify the maximum follow-up time ($T_{follow-up}$), mean interpatient arrival time ($MIAT$) and inevaluable rate ($IR$) for the enrollment simulation. See Figure 1.2. Hover mouse over each trial parameter, and a description will be displayed explaining the meaning of the parameter. The detailed explanation of the above three input arguments is provided in Table 1.1. The technical details of simulating patients enrollment is provided in §1.3.1.

![Step 1: Set enrollment parameters](image)

Figure 1.2: Set enrollment parameters in the Single-Agent Dose-Finding Designs with Toxicity Endpoint and Rolling Enrollment.

Table 1.1: Input arguments for enrollment parameters in the Single-Agent Dose-Finding Designs with Toxicity Endpoint and Rolling Enrollment.

<table>
<thead>
<tr>
<th>Notation</th>
<th>Parameters</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_{follow-up}$</td>
<td>The maximum follow-up time</td>
<td>The DLT observation period for each patient in the trial (days). Default value is 21 days.</td>
</tr>
<tr>
<td>$MIAT$</td>
<td>Mean interpatient arrival time</td>
<td>The mean chronologic time (days) for a patient to arrive in the clinic and be eligible for study. Default value is 10 days.</td>
</tr>
<tr>
<td>$IR$</td>
<td>Inevaluable rate</td>
<td>The proportion of patients who entered the trial and received the treatment, but dropped out due to non-DLT related event when being followed up. Default value is 0.1.</td>
</tr>
</tbody>
</table>
Module 1. Single-Agent Dose-Finding Designs with Toxicity Endpoint and Rolling Enrollment

1.2.2.2 Step 2: Set trial parameters

Specify the target toxic probability ($p_T$), number of simulations ($n_{sim}$), and random seed of simulation ($R_{seed}$) for the simulated trials. See Figure 1.3. Hover mouse over each trial parameter, and a description will be displayed explaining the meaning of the parameter. The detailed explanation of the above three input arguments is provided in Table 1.2.

![Step 2: Set trial parameters](image)

Figure 1.3: Set trial parameters in the Single-Agent Dose-Finding Designs with Toxicity Endpoint and Rolling Enrollment.

<table>
<thead>
<tr>
<th>Notation</th>
<th>Parameters</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$p_T$</td>
<td>Target toxicity probability</td>
<td>The target toxicity probability of the maximum tolerated dose (MTD). The main objective of phase I clinical trials is to find the highest dose with a toxicity probability closest to or lower than $p_T$. Default value is 0.3.</td>
</tr>
<tr>
<td>$n_{sim}$</td>
<td>The number of simulated trials</td>
<td>The maximum number of simulated trials allowed is 10,000. Default value is 1,000.</td>
</tr>
<tr>
<td>$R_{seed}$</td>
<td>The random seed of simulation</td>
<td>A random seed is a number used to initialize a pseudorandom number generator in the simulation. Default value is 32432.</td>
</tr>
</tbody>
</table>
1.2. User Interface and Tutorial

1.2.2. Simulation Setup

1.2.2.3 Step 3: Select designs

To select a design, click the button with the design’s name on it. Up to four design configurations may be selected for comparison.

When setting the sample size $n$ for the mTPI-2 and R-TPI designs, two options are provided: 1) match with 3+3, if a 3+3 design is selected; 2) manually input. Check the “Match with 3+3” box to use the average sample size of the selected 3+3 design as the maximum sample size $n$. If two or more 3+3 design configurations are selected, U-Design would choose the first 3+3 design in the design list as the benchmark. Figure 1.4 is an example if one selects mTPI-2, 3+3, rolling six and R-TPI designs, with the sample size of mTPI-2 matching with 3+3 and the sample size of R-TPI being a manually input value, 30.

Click the “Delete” button to remove the selected designs.

Design parameters can be modified in the input box of corresponding row. Hover mouse over each design parameter, and a description will be displayed explaining the meaning of the parameter. See detailed parameter descriptions in Table 1.3.

![Design Selection](image)

**Figure 1.4**: Select designs in the **Single-Agent Dose-Finding Designs with Toxicity Endpoint and Rolling Enrollment**.
Table 1.3: Input parameters for designs in the Single-Agent Dose-Finding Designs with Toxicity Endpoint and Rolling Enrollment.

<table>
<thead>
<tr>
<th>Notation</th>
<th>Parameters</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$d_{\text{start}}$ (all designs)</td>
<td>Starting dose level</td>
<td>The starting dose level in the simulated trials. Default value is 1.</td>
</tr>
<tr>
<td>$n$ (all designs)</td>
<td>Sample size</td>
<td>The maximum number of patients to be treated in the trial. The upper limit is set at 100 since the number of patients that are enrolled in phase I clinical trial is typically small. Default value is 30.</td>
</tr>
<tr>
<td>$\epsilon_{1}, \epsilon_{2}$ (mTPI-2, R-TPI)</td>
<td>$\epsilon_{1}$: lower margin $\epsilon_{2}$: higher margin</td>
<td>Two small fractions used to define the equivalence/target interval of the MTD. Any dose with a toxicity probability falling into the interval $[p_{T} - \epsilon_{1}, p_{T} + \epsilon_{2}]$ is considered an acceptable dose of MTD. Default values for both are 0.05.</td>
</tr>
<tr>
<td>$n_{\text{cohort}}$ (mTPI-2)</td>
<td>Cohort size</td>
<td>The number of patients in each cohort. Default value is 3. For 3+3, the cohort size is 3 by default, and for Rolling 6 and R-TPI designs, there is no concept of cohort size and patients are enrolled as needed without suspension.</td>
</tr>
<tr>
<td>$C$ (R-TPI)</td>
<td>The maximum number of pending patients allowed in the trial</td>
<td>The maximum number of pending patients without observed outcomes allowed in the trial. It can be provided by users to control the enrollment speed. For rolling six design, $C$ is 6 by default.</td>
</tr>
</tbody>
</table>
1.2. User Interface and Tutorial

1.2.2. Simulation Setup

1.2.2.4 Step 4: Generate scenarios

There are two ways to generate scenarios, automatically (in below Auto Generation tab, see Figure 1.5) or through manual construction (in below Manual Construction tab, see Figure 1.6). Once scenarios are generated, click the “Launch Simulation” button at the bottom of the page to run \( n_{sim} \) (set in step 2) simulations, for each scenario and selected design (set in step 3) combination, assuming \( p_T \) (set in step 2) and patients enrollment and follow-up conditions, \( T_{\text{follow-up}} \), MIAT and IR (set in step 1).

**Auto Generation** (Figure 1.5)

Select the number of doses \( n_{dose} \) (3 \( \leq n_{dose} \leq 10 \)) from the dropdown box. Upon selection, five or six scenarios will be created automatically, each of which contains the true toxicity probabilities for \( n_{dose} \) dose levels. These generated scenarios are displayed and editable. The detailed algorithm for scenarios auto generation is provided next.

**Manual Construction** (Figure 1.6)

Follow the instructions below to manually construct scenarios. Then click the “Add” button to create these scenarios. The format of input must comply with the following instructions.

- Scenarios should be separated by line breaks;
- The parameters in one scenario should be ordered in accordance with this sequence:
  
  Target toxicity probability, Number of simulated trials, True toxicity probabilities of all the dose levels;

- Each parameter must be separated by a white space or comma.

For example, by inputting “0.2 1000 0.05 0.1 0.15 0.2” or “0.2,1000,0.05,0.1,0.15,0.2”, a scenario is presented that runs 1000 simulated trials with a target \( p_T = 0.2 \) and true toxicity probabilities of four dose levels, 0.05, 0.1, 0.15 and 0.2.

The generated scenarios are displayed as a list (Figures 1.5 and 1.6) which appears below the generation section. An interactive chart will also be generated to visually display the shape of true toxicity probabilities for each scenario.
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Figure 1.5: Automatically generate scenarios in the Single-Agent Dose-Finding Designs with Toxicity Endpoint and Rolling Enrollment module.

Figure 1.6: Manually generate scenarios in the Single-Agent Dose-Finding Designs with Toxicity Endpoint and Rolling Enrollment module.
Algorithm for Auto Generation

By entering the number of candidate dose levels $n_{\text{dose}}$, five or six scenarios are generated automatically. See Figure 1.7 for an illustration. They represent the four types of dose-response shapes below.

<table>
<thead>
<tr>
<th>Types</th>
<th>Dose-Response Shape</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ideal</td>
<td>Some doses are tolerable but some are overly toxic, AND there exists at least one dose level close to the target $p_T$ or falling within the equivalence interval $[p_T - \epsilon_1, p_T + \epsilon_2]$.</td>
</tr>
<tr>
<td>Safe</td>
<td>All doses are safe and tolerable with the true toxicity probabilities smaller than the target $p_T$ or the lower boundary of equivalence interval $(p_T - \epsilon_1)$.</td>
</tr>
<tr>
<td>Toxic</td>
<td>All doses are overly toxic with the true toxicity probabilities larger than the target $p_T$ or the upper boundary of equivalence interval $(p_T + \epsilon_2)$.</td>
</tr>
<tr>
<td>Steep</td>
<td>Some doses are tolerable but some are overly toxic, AND there is a steep jump in the toxicity probability between two adjacent doses, AND there is no dose close to the target $p_T$ or falling within the equivalence interval $[p_T - \epsilon_1, p_T + \epsilon_2]$.</td>
</tr>
</tbody>
</table>

Two “Steep” scenarios are generated, with the toxicity probability steep jump occurring at the first or second half of the doses. Similarly, two “Ideal” scenarios might be generated, with the MTD placed in the first or second half of the doses.
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**Figure 1.7:** An example of four main types of scenarios. Five dose levels are considered for escalation. The target toxicity probability is $p_T = 0.25$, and the equivalence interval is $EI=[0.2, 0.3]$. Six different lines represent four main types of scenario, respectively. In “Ideal” scenarios (Lines 1 and 2), doses 2 and 4 are the true MTD with toxicity probability falling within the EI, respectively. In “Safe” scenario (Line 3), all doses are safe with toxicity probabilities smaller than the target $p_T = 0.25$. “Toxic” scenario (Line 4) gives a contrary situation to the “Safe” scenario, where all doses are overly toxic with the toxicity probabilities larger than the target $p_T = 0.25$. The remaining two lines (Lines 5 and 6) are “Steep” scenario, in which some doses are tolerable but some are overly toxic and there is a steep jump in the toxicity probability occurring at the first or second half of the doses (between doses 4 and 5 in Line 5, and between doses 1 and 2 in Line 6).
1.2.2.5 Launch simulation

Once the steps 1-4 are completed, users can conduct simulated clinical trials to examine the operating characteristics of the selected designs using the selected scenarios, by clicking the “Launch Simulation” button at the bottom of Simulation Setup tab (Figures 1.5 and 1.6). A green “Launch Successful” message will be displayed on the website as in Figure 1.8 to indicate that the simulation has been successfully launched. Users may click the “Proceed To Simulation Results” button in the pop-up box to track the simulation processing status and simulation results.

![Launch Successful message](image)

**Figure 1.8:** “Launch Successful” message after launching simulation in the Single-Agent Dose-Finding Designs with Toxicity Endpoint and Rolling Enrollment module.
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1.2.3 Simulation Results

In the Simulation Results tab, users can view the simulation progress and simulation results (§1.2.3.1), restore the simulation settings if needed (§1.2.3.2), and download intelligent simulation reports (§1.2.3.3). Specifically, all the simulation results (figures and tables) can be downloaded in Word format. Hereinafter, we use simulation results and operating characteristics interchangeably.

1.2.3.1 View simulation results

In the Simulation Results tab, the Running Simulations panel exhibits the progress of ongoing simulation (Figure 1.9). The ongoing simulations are displayed in ascending order by the launch time. Click the icon “×” to delete the corresponding simulation.

![Running Simulations panel](image)

Figure 1.9: Simulation progress in the Single-Agent Dose-Finding Designs with Toxicity Endpoint and Rolling Enrollment module.

Once the simulations are completed, the Running Simulations panel in Figure 1.9 will disappear, a green “simulation result created” massages will appear instead and stay at the same place of the Running Simulations panel unless explicitly dismissed by clicking the icon “×” at the end of the corresponding row, and the simulation results will be automatically loaded into the Simulation History panel (Figure 1.10), with the blue mail icon 🔄 shown to indicate new results. All the previously completed simulations are also listed in the Simulation History panel. Simulation results for other modules can also be viewed under the Simulation History by dropping down the “Select a module” button (Figure 1.10). Click the button to delete the selected simulation results.
1.2. User Interface and Tutorial
1.2.3. Simulation Results

Figure 1.10: Simulation Results in the Single-Agent Dose-Finding Designs with Toxicity Endpoint and Rolling Enrollment module.

Click the button to unfold the simulation results (Figure 1.10). The design settings are firstly displayed at the top of each simulation study (Figure 1.11). Then the results of simulation are shown as plots and tables below.

Figure 1.11: View the simulation results in the Single-Agent Dose-Finding Designs with Toxicity Endpoint and Rolling Enrollment module.
Simulation Result Plots

There are two sections in the Simulation Result Plots:

A. Line plots showing six summary statistics of the simulation results for all the designs (Figure 1.12), including Prob. of Selecting MTD, Prob. of Toxicity, Prob. of Selecting Does-over-MTD, Prob. of No Selection, Trial Duration and Average Number of Enrolled Patients.

B. A table of mean and standard deviation (s.d.) for the six summary statistics (Figure 1.13).

A. Line plots:

- The six summary statistics are part of operating characteristics of the designs. They are explained in full detail next.

  - **Prob. of Selecting MTD**: The probability of selecting the true MTD, defined as the proportion of simulated trials that correctly select the true MTD. The higher the value, the better the design.

    * For interval-based designs (mTPI-2 & R-TPI), the true MTDs are defined as the dose levels of which the true toxicity probabilities fall into the equivalence interval \([p_T - \epsilon_1, p_T + \epsilon_2]\); if none of the doses have a toxicity probability that falls into the equivalence interval, the true MTD is defined as the dose with the highest toxicity probability below \(p_T\). For the non-interval-based designs, 3+3 and Rolling 6, the true MTDs is defined as the dose levels with the highest toxicity probabilities lower than or equal to \(p_T\).

    * To compare the operating characteristics of multiple designs submitted in a simulation study, the definition of MTD should be unified. If any of interval-based designs (mTPI-2 & R-TPI) are used in the simulation, the dose levels of which the true toxicity probabilities fall into the widest equivalence interval \([p_T - \max\{\epsilon_1\}, p_T + \max\{\epsilon_2\}]\) are defined as the true MTDs. Here, \(\max\{\cdot\}\) is taken over the designs. If none of the doses fall in, the dose with the highest toxicity probability that is below \(p_T\) is the true MTD. For example, consider a case in which users compare four designs, R-TPI, mTPI-2, Rolling 6 and 3+3, in a simulation study targeting \(p_T = 0.3\). Suppose \(\epsilon_1 = 0.02\) and \(\epsilon_2 = 0.05\) for R-TPI, and \(\epsilon_1 = 0.05\) and \(\epsilon_2 = 0.03\) for mTPI-2. In this case, the true MTD is the dose levels with toxicity probabilities in \([0.3 - 0.05, 0.3 + 0.05]\); if none of the doses have a toxicity probability in \([0.3-0.05, 0.3+0.05]\), the dose with the highest toxicity probability lower than 0.3 is the true MTD.

    * If a scenario does not have any MTD (e.g., all doses have toxicity probabilities...
larger than the target \( p_T \), no selection is the right decision. In this case, the probability of selecting the true MTD is the probability of no selection.

- **Prob. of Toxicity**: The proportion of patients who have experienced DLT across all the simulated trials. The lower the number, the fewer patients having DLTs under the design.

- **Prob. of Selecting Does-over-MTD**: The probability of selecting the dose levels above the true MTD, which is defined by the proportion of simulated trials that select a dose higher than the true MTD at the end of the trial. The lower the value, the better the safety of the design.

- **Prob. of No Selection**: The proportion of the simulated trials in which none of the dose levels are selected as the MTD. If a scenario does not have any MTD, this values is treated as the probability of selecting the true MTD.

- **Average Trail Duration**: The average time duration for trial conduct (in days). The lower the value, the faster the trials and the more economic of the design.

- **Average Number of Enrolled Patients**: The average number of patients enrolled in the trial, including the patients who complete the DLT observation period with DLT or non-DLT, and patients who drop out of the trial and become inevaluable for DLTs.

  - For each line plot, the x-axis is the index of scenario and the y-axis is the value of summary statistics. Lines with different colors represent different designs.
  
  - The plots are interactive for better visualization.
    
    - Hover the mouse on a dot and a box will display the value of each design at the corresponding scenario (e.g. top left plot in Figure 1.12: Prob. of Selecting MTD)
    
    - Hover the mouse on the design label to highlight the corresponding line and fade the others (e.g. bottom right plot in Figure 1.12: Average Number of Enrolled Patients).
    
    - Click the design label to hide the corresponding line and click again to change it back (e.g. bottom right plot in Figure 1.12: Average Number of Enrolled Patients).

B. Simulation summary table: Figure 1.13 shows the mean±sd of the summary statistics across all scenarios for each design.
Figure 1.12: Simulation result plots in the Single-Agent Dose-Finding Designs with Toxicity Endpoint and Rolling Enrollment module.

Figure 1.13: Simulation summary table in the Single-Agent Dose-Finding Designs with Toxicity Endpoint and Rolling Enrollment module.
Simulation Result Tables

Full simulation results are presented in tabular format arranged by scenarios (Figure 1.14).

In the upper part of Figure 1.14, the first two columns summarize dose levels and their true toxicity probabilities; the remaining columns report three dose-specific summary statistics from the simulations: selection probability, average number of patients treated, and average number of toxicities (i.e. DLTs), along with their standard deviations, at each dose level. Specifically, they are

1) **Selection Prob.**: The proportion of simulated trials that select each dose level as the MTD.
2) **# of Patients Treated (s.d.)**: The average number of patients treated at each dose level.
3) **# of Toxicities (s.d.)**: The average number of patients experienced DLT at each dose level.

The true MTD(s) of the scenario is(are) highlighted by the orange bar. For the definition of the true MTD in the simulation results, please refer to the definition of **Prob. of Selecting MTD** in the Simulation Results Plots above (after Figure 1.11).

In the lower part of Figure 1.14, more trial-specific summary statistics are reported, mainly from four aspects: **MTD Selection, Trial Toxicity, Trial Duration** and **Trial Sample Size**.

- **MTD Selection**
  - **Prob. of Selecting MTD**: The proportion of simulated trials that select the true MTD at the end of the trial.
  - **Prob. of Selecting Does-over-MTD**: The proportion of simulated trials that select the doses higher than the true MTD at the end of the trial.
  - **Prob. of No Selection**: The proportion of simulated trials in which none of the dose levels are selected as the MTD. If a scenario does not have any MTD, this values is treated as the probability of selecting the true MTD.

For detailed descriptions, please refer to **Simulation Result Plots** section above (after Figure 1.11).

- **Trial Toxicity**
  - **Prob. of Toxicity**: The proportion of patients experiencing DLT across all the simulated trials. For detailed descriptions, please refer to **Simulation Result Plots** section above (after Figure 1.11).

- **Trial Duration**
  - **Average Trial Duration (s.d.)**: The average time duration for trial conduct (in days) and its standard deviation.

- **Trial Sample Size**
  - **Average # of Patients Treated (s.d.)**: The average number of patients treated in the
simulated trials and its standard deviation. Due to early stopping, this number is lower
than or equal to $n$.

When calculating the standard deviation, we use $n_{\text{sim}}$ as the denominator instead of $(n_{\text{sim}} - 1)$
in U-Design.

---

**Scenario 1**

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>True Prob.</th>
<th>Selection Prob.</th>
<th># of Patients Treated</th>
<th># of Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.15</td>
<td>0.405</td>
<td>0.524</td>
<td>0.446</td>
</tr>
<tr>
<td>2</td>
<td>0.3</td>
<td>0.288</td>
<td>0.48</td>
<td>0.615</td>
</tr>
<tr>
<td>3</td>
<td>0.45</td>
<td>0.067</td>
<td>0.183</td>
<td>0.058</td>
</tr>
<tr>
<td>4</td>
<td>0.6</td>
<td>0.039</td>
<td>0.022</td>
<td>0.021</td>
</tr>
<tr>
<td>5</td>
<td>0.75</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
</tr>
</tbody>
</table>

**Scenario 2**

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>True Prob.</th>
<th>Selection Prob.</th>
<th># of Patients Treated</th>
<th># of Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.08</td>
<td>0.222</td>
<td>0.068</td>
<td>0.215</td>
</tr>
<tr>
<td>2</td>
<td>0.16</td>
<td>0.111</td>
<td>0.241</td>
<td>0.333</td>
</tr>
<tr>
<td>3</td>
<td>0.24</td>
<td>0.208</td>
<td>0.558</td>
<td>0.216</td>
</tr>
<tr>
<td>4</td>
<td>0.3</td>
<td>0.125</td>
<td>0.526</td>
<td>0.177</td>
</tr>
<tr>
<td>5</td>
<td>0.38</td>
<td>0.076</td>
<td>0.068</td>
<td>0.048</td>
</tr>
</tbody>
</table>

The row with a background color indicates the TRUE MTD.

**Figure 1.14:** Simulation result tables in the Single-Agent Dose-Finding Designs with Toxicity Endpoint and Rolling Enrollment module.
1.2.3.2 Restore simulation

Users can restore the simulation settings from the simulation results by clicking the “Restore” button at the upper right corner of each simulation results panel (yellow arrow in Figure 1.15). Upon clicking, the display will switch to the Simulation Setup page with the same simulation settings restored. This is useful to restore the old simulation settings for reproducible results.

![Simulation Setup interface]

**Figure 1.15:** Restore simulation setup and download simulation results in the Single-Agent Dose-Finding Designs with Toxicity Endpoint and Rolling Enrollment module.

1.2.3.3 Download simulation results

There is a “Download Report” button at the upper right corner of each simulation results panel (green arrow in Figure 1.15). Click it to download a word file, which includes three parts:

- Part A: Complete simulation results under the designs and scenarios users added in the Simulation Setup tab;
- Part B: Detailed technical descriptions of the designs users added in the Simulation Setup tab;
- Part C: Reference

Users may select the required parts and modify them tailored for their trials or contact us via email (admin@laiyaconsulting.com) for consulting services.
1.2.4 Decision Table

In the Decision Table tab, users can generate decision tables of mTPI-2 and 3+3 designs, to guide the dose escalation/de-escalation during trial conduct. The decision tables of Rolling 6 and R-TPI can also be pretabulated, but are much more complicated, so U-Design do not provide them in current version.

Manually type in the maximum number of patients at a dose \( (n) \), target toxicity probability \( (p_T) \) and two small fractions \( (\epsilon_1 \) and \( \epsilon_2) \) for decision table generation (Figure 1.17). Hover mouse over each parameter, and a description will be displayed explaining the meaning of the parameter. See detailed parameter descriptions in Table 1.4.

![Figure 1.16: Input parameters in the Decision Table tab of Single-Agent Dose-Finding Designs with Toxicity Endpoint and Rolling Enrollment module.](image)

Click the “Generate” button to generate five decision tables for two different designs at the same time (Figure 1.17). Users can click the tabs to switch between the tables for the mTPI-2 and 3+3 designs.

Click the “Download Decision Table” button to save the decision table of the corresponding design in word (.docx).

For each decision table, the column represents the number of patients treated at a dose, which is mostly used for the current dose, the dose currently being used to treat patients in the trial, and the row represents the number of patients among those treated at that dose who have experienced dose-limiting toxicity (DLT) events. Note that these are the counts of patients, not DLT events. For example, column 3 and row 1 means that 3 patients have been treated at the current dose and 1 of them experiences DLT. Each cell in the decision table provides the dose-assignment decision based on the readouts from the corresponding row and column. For example, for column 3 and row 1, i.e., 1 out of 3 patients experiences DLTs, the decision is “S”. The letters in the decision table represent different dose-assignment decisions as shown below:
### Table 1.4: Input arguments in the Decision Table tab of Single-Agent Dose-Finding Designs with Toxicity Endpoint and Rolling Enrollment module.

<table>
<thead>
<tr>
<th>Notation</th>
<th>Parameters</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$n$</td>
<td>Number of patients at a dose</td>
<td>The maximum number of patients to be treated at a dose. Here, the upper limit is set at 30 since the number of patients that are enrolled at a dose in phase I clinical trial is typically small.</td>
</tr>
<tr>
<td>$p_T$</td>
<td>Target toxicity probability</td>
<td>The target toxicity probability of the maximum tolerated dose (MTD). The main objective of phase I clinical trials is to find the highest dose with a toxicity probability closest to or lower than $p_T$.</td>
</tr>
<tr>
<td>$\epsilon_1, \epsilon_2$</td>
<td>$\epsilon_1$: lower margin, $\epsilon_2$: higher margin</td>
<td>Two small fractions used to define the equivalence/target interval of the MTD. Any dose with a toxicity probability falling into the interval $[p_T - \epsilon_1, p_T + \epsilon_2]$ is considered an acceptable dose MTD. Default values for both are 0.05.</td>
</tr>
</tbody>
</table>

- “E” stands for escalating to the next higher dose,
- “S” stands for staying at the current dose,
- “D” stands for de-escalating to the previous lower dose,
- “DU” stands for de-escalating to the previous lower dose and marking the current dose and its higher doses as unacceptably toxic so that they will never be used again in the remainder of the trial.

The 3+3 decision table is fixed regardless of different trial parameters. For rolling six and R-TPI designs, their decisions are not only based on the number of patients treated at a dose and the number of patients having already experienced DLT events among them, but also on the number of patients who are still being followed without outcomes. See the decision table of the rolling six in Table 1.6 (§1.3.4). See an example of R-TPI decision table in Table 1.8 (§1.3.5).
<table>
<thead>
<tr>
<th>mTPI-2</th>
<th>mTPI</th>
<th>mCCD</th>
<th>3+3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Figure 1.17**: Decision tables generated in the **Single-Agent Dose-Finding Designs with Toxicity Endpoint and Rolling Enrollment** module.
1.2.5 MTD Estimation

In the MTD Estimation tab, users can estimate the MTD for mTPI-2 and R-TPI designs based on the isotonic regression through Pool Adjacent Violators Algorithm (PAVA), after the dose finding is completed and the DLT outcomes of all patients are collected.

Specify the target toxicity probability ($p_T$), and two small fractions to define the equivalence interval ($\epsilon_1$ and $\epsilon_2$) in the design. Select the number of doses ($n_{dose}$) from the dropdown box, then an editable table will be shown below on the page (Figure 1.18). Then manually type in the observed number of toxicities (DLTs) and the number of patients treated at each dose into the table and click the “Estimate” button to estimate the MTD. Finally, the estimated MTD is highlighted in blue background as shown in Figure 1.19.

Hover mouse over each parameter, and a description will be displayed explaining the meaning of the parameter. See detailed parameter descriptions in Table 1.5.

![Figure 1.18: Input parameters in the MTD Estimation tab of Single-Agent Dose-Finding Designs with Toxicity Endpoint and Rolling Enrollment module.](image)

![Figure 1.19: MTD estimation in the Single-Agent Dose-Finding Designs with Toxicity Endpoint and Rolling Enrollment module.](image)
Table 1.5: Input parameters in the MTD Estimation tab of Single-Agent Dose-Finding Designs with Toxicity Endpoint and Cohort Enrollment module.

<table>
<thead>
<tr>
<th>Notation</th>
<th>Parameters</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$p_T$</td>
<td>Target toxicity probability</td>
<td>The target toxicity probability of the maximum tolerated dose (MTD). The main objective of phase I clinical trials is to find the highest dose with a toxicity probability closest to or lower than $p_T$.</td>
</tr>
<tr>
<td>$\epsilon_1, \epsilon_2$</td>
<td>$\epsilon_1$: lower margin $\epsilon_2$: higher margin</td>
<td>Two small fractions used to define the equivalence/target interval of the MTD. Any dose with a toxicity probability falling into the interval $[p_T - \epsilon_1, p_T + \epsilon_2]$ is considered an acceptable dose MTD. Default values for both are 0.05.</td>
</tr>
<tr>
<td>$n_{dose}$</td>
<td>The number of doses</td>
<td>The number of candidate dose levels for investigation</td>
</tr>
<tr>
<td># of DLTs</td>
<td>The number of patients with DLTs at each dose level</td>
<td>A non-negative integer number of patients with DLT at each dose level</td>
</tr>
<tr>
<td># of patients</td>
<td>The number of patients treated at each dose level</td>
<td>A positive integer number of patients treated at each dose level, which should be no less than the # of DLTs</td>
</tr>
</tbody>
</table>
1.3 Statistical Methods Review

1.3.1 Simulating Patients Enrollment and Evaluation

To better demonstrate the benefit of rolling-based designs in accelerating the trial conduct, trial duration would be assessed, in addition to the operating characteristics of the safety and reliability. Therefore, this module simulates trials based on a real-life setting, in order to better reflect the real-world situation. Figure 1.20 illustrates the simulation process of patients enrollment and evaluation. Specifically,

1. Each patient is assigned an inter-patient arrival time (a chronological time for a patient to arrive in the clinic and be eligible for study). The inter-patient arrival time is sampled from gamma distribution, with the shape parameter of $a$ and scale parameter of $b$. So the mean inter-patient arrival time (MIAT) is $\text{MIAT} = ab$. For example, MIAT is 10 or 5 days means on average three or six patients per month will arrive in the clinic and be eligible for study, respectively.

2. To mimic real-life oncology dose-finding trials, each enrolled patient in the simulation study is also assigned an on-study start time (the gap between the time of arrival in the clinic and the starting time of treatment) and the probability of inevaluability (such as drop off).
   
   (a) A random binary DLT/non-DLT outcome generated with the true probability of toxicity for the corresponding dose at which the patient is assigned.
   
   (b) A random binary evaluability/inevaluability outcome generated with the inevaluable rate (IR) of the enrolled patient.
   
   (c) The on-study start time is sampled from the uniform distribution ranging from 0 to the maximum waiting time.
   
   (d) If a DLT occurs in that patient, the time to DLT is sampled from the uniform distribution ranging from 0 to the maximum DLT follow-up period $T_{\text{follow-up}}$; Otherwise, the time to non-DLT is $T_{\text{follow-up}}$.
   
   (e) If that patient becomes inevaluable, the time to inevaluability (IE) of that patient is sampled from a uniform distribution ranging from 0 to the sampled time to event (either DLT or non-DLT) of that patient.

Therefore, assume that the trial starts at the time $t = 0$ (i.e., the first patient arrives and is available for study at the time $t = 0$), a patient complete the trial with the event (DLT, non-DLT, or IE) at the time $t_i = \text{The arrival time} + \text{The on-study start time} + \text{The time to DLT or non-DLT or IE}$. 

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Module 1. Single-Agent Dose-Finding Designs with Toxicity Endpoint and Rolling Enrollment

In U-Design, we fix $a = 1$ in sampling the inter-patient arrival time, so the mean inter-patient arrival time is $\text{MIAT} = b$. And also, for simplicity, we assume that there is no waiting time between the time of patient arrival in the clinic and the starting time of treatment, so the on-study start time is 0.

**Figure 1.20:** Simulating patients enrollment and evaluation in the Single Agent – Rolling-Based Designs.
1.3.2 The 3+3 Design

The 3+3 design (Storer, 1989) is a rule-based design which enrolls patients in a cohort of three. It starts by allocating the first cohort of three patients to the starting dose (which is often the lowest dose level) and adaptively escalates/de-escalates to the next dose level based on observed number of dose limiting toxicities (DLTs). Besides, in this module, the ethics constraint of “decision-in-advance” (§1.3.2.2) is adopted, which is applicable to the real-life trials.

1.3.2.1 Design Algorithm

In 3+3, a maximum of six patients are allowed to be treated at any dose level, and the MTD is defined as the highest dose for which one or fewer DLTs occurred in six patients. Its algorithm proceeds as follows:

0. Start the trial by treating three patients at a prespecified starting dose level.
1. Escalate to the next higher dose or de-escalate to the previous lower dose according to the following rules:
   
   (a) If 0 of 3 patients has a DLT, escalate to next higher dose and treat three patients.
   (b) If 2 or more of 3 patients have DLTs, de-escalate to previous lower dose and treat three patients.
   (c) If 1 of 3 patients has a DLT, treat three more patients at current dose level.
      i. If 1 of 6 has DLT, escalate to next higher dose and treat three patients if the next higher dose has not been tried; otherwise, declare it as the MTD and stop the trial.
      ii. If 2 or more of 6 have DLTs, de-escalate to previous lower dose level and treat three patients.
   (d) If the trial de-escalates to previous lower dose:
      i. If only 3 or less had been treated at the previous lower dose, treat three more patients at that dose.
      ii. If six have already been treated at the previous lower dose, stop the trial and declare the lower dose as the MTD.

2. Escalation never occurs to a dose at which two or more DLTs have already occurred.
3. If de-escalation occurs at the lowest dose, the trial is stopped.
4. Repeat steps 1-3 until either the MTD is identified or the trial is stopped for excessive toxicity.
1.3.2.2 The “Decision-in-Advance” Rule

If a cohort of patients for the current dose is not fully enrolled or completely observed, a decision can be made in advance if and only if the decision would not be changed by the pending data for the cohort of patients, either enrolled but still being followed or yet to be enrolled. For example, under 3+3, if 2 patients have been enrolled to a newly used dose \( d \) and both of them experience DLTs, stop enrolling the third patient to \( d \) and de-escalate to \( d - 1 \) immediately. This rule of “decision-in-advance” can accelerate the trial and make the trial conduct more ethical.
1.3.3 The Modified Toxicity Probability Interval-2 (mTPI-2) Design

The modified toxicity probability interval-2 (mTPI-2) design (Guo et al., 2017) is a cohort-based design which enrolls patients according to a pre-planned cohort size. It is also a model-base design, which uses a simple beta-binomial model to estimate the toxicity probability and makes dose escalation/de-escalation decisions based on the unit probability mass (UPM) of a series of dosing interval with equal length. At the end, mTPI-2 selects the dose of which the isotonic transformed toxicity probability is the closest to the target $p_T$ as the MTD. Besides, in this module, the ethics constraint of “decision-in-advance” (§1.3.3.3) is adopted, which is applicable to the real-life trials.

1.3.3.1 Probability Model

Consider a phase I trial with $D$ candidate doses for escalation. Let $p_1, \ldots, p_D$ denote the true toxicity probabilities for doses $d = 1, \ldots, D$. The observed data include $n_d$, the number of patients treated at dose $d$, and $y_d$, the number of patients experiencing a toxicity. Let $Data = \{(y_d, n_d); d = 1, 2, \ldots, D\}$.

The mTPI-2 design employs a simple beta-binomial hierarchical model as follow:

$$y_d \mid n_d, p_d \sim \text{binomial}(n_d, p_d)$$

$$p_d \sim \text{beta}(\alpha, \beta)$$

The posterior distribution of $p_d$ is given by

$$p_d \mid y_d, n_d \sim \text{beta}(\alpha + y_d, \beta + n_d - y_d).$$  \hspace{1cm} (1.1)

In U-Design, we adopt the prior $\text{beta}(1, 1)$ for $p_d$, because it would lead to slightly conservative posterior inference as the prior mean is 0.5, which is usually above $p_T$.

1.3.3.2 Dose-Finding Rules

Equal-width Dosing Intervals: The mTPI-2 design improves over the mTPI design (Ji et al., 2010) by blunting the Ockhams razor that leads to some statistically sound but practically debatable decisions in mTPI. In mTPI, the unit interval $(0, 1)$ is divided into three intervals: the under-dosing interval $(0, p_T - \epsilon_1)$, the equivalence interval $(p_T - \epsilon_1, p_T + \epsilon_2)$, and the over-dosing interval $(p_T + \epsilon_2, 1)$. Here, $\epsilon_1$ and $\epsilon_2$ are small fractions, such as 0.05, to account for the uncertainty around the true target toxicity $p_T$. However, mTPI-2 resolves the the Ockhams razor problem fundamentally by dividing the intervals $(0, p_T - \epsilon_1)$ and $(p_T + \epsilon_2, 1)$ into shorter subintervals with length $(\epsilon_1 + \epsilon_2)$,
which is the same as the length of the equivalence interval, to mitigate the effect of interval length in the mTPI design. For clarify, denote $EI$ the equivalence interval $(p_T - \epsilon_1, p_T + \epsilon_2)$, and $LI$ a set of intervals below $EI$,

$$LI = \{M_{LI}^{1} = (p_T - 2\epsilon_1 - \epsilon_2, p_T - \epsilon_1), M_{LI}^{2} = (p_T - 3\epsilon_1 - 2\epsilon_2, p_T - 2\epsilon_1 - \epsilon_2), \ldots, M_{LI}^{J} = (0, p_T - J\epsilon_1 - (J - 1)\epsilon_2)\},$$

and $HI$ a set of intervals above $EI$,

$$HI = \{M_{HI}^{1} = (p_T + \epsilon_2, p_T + \epsilon_1 + 2\epsilon_2), M_{HI}^{2} = (p_T + \epsilon_1 + 2\epsilon_2, p_T + 2\epsilon_1 + 3\epsilon_2), \ldots, M_{HI}^{K} = (p_T + (K - 1)\epsilon_1 + K\epsilon_2, 1)\}.$$

For example, if $p_T = 0.3$ and $\epsilon_1 = \epsilon_2 = 0.05$,

$$EI = (0.25, 0.35)$$

$$LI = \{M_{LI}^{1} = (0.15, 0.25), M_{LI}^{2} = (0.05, 0.15), M_{LI}^{3} = (0, 0.05)\},$$

$$HI = \{M_{HI}^{1} = (0.35, 0.45), M_{HI}^{2} = (0.45, 0.55), M_{HI}^{3} = (0.55, 0.65), M_{HI}^{4} = (0.65, 0.75),$$

$$M_{HI}^{5} = (0.75, 0.85), M_{HI}^{6} = (0.85, 0.95), M_{HI}^{7} = (0.95, 1)\}.$$ 

Other than the boundaries $(0, 0.05)$ and $(0.95, 1)$, all the intervals have the same length. The boundaries do not affect the decision making since they are clearly associated with “E” and “D” decisions, respectively. See Guo et al. (2017) for details.

**Dose-Finding Rules:** Given the interval and a probability distribution like (1.1), define the unit probability mass (UPM) of that interval as the probability of the interval divided by the length of the interval. Mathematically, the UPM of an interval $(a, b)$ equals to

$$\text{UPM} = \frac{\text{Prob}\{p \in (a, b) \mid Data\}}{b - a}$$

The mTPI-2 selects the (sub-)interval with the largest UPM value as the winning interval and take the dose-escalation decision corresponding to the winning (sub-)interval. More specifically,

- If the equivalence interval $M^{EI} = (p_T - \epsilon_1, p_T + \epsilon_2)$ has the largest UPM, it is selected as the winning interval and dose-assignment decision of mTPI-2 is “S”, to stay at the current dose.
- If any interval $M_{LI}^{j}$ in $LI$ has the largest UPM, it is selected as the winning interval and dose-assignment decision of mTPI-2 is “E”, to escalate to the next higher dose.
- If any interval $M_{HI}^{k}$ in $HI$ has the largest UPM, it is selected as the winning interval and dose-assignment decision of mTPI-2 is “D”, to de-escalate to the previous lower dose.
1.3.3.3 The “Decision-in-Advance” Rule

If a cohort for the current dose is not fully enrolled or completely observed, a decision can be made in advance if and only if the decision would not be changed by the pending data for the cohort of patients, either enrolled but still being followed or yet to be enrolled. For example, under $p_T = 0.3$, if 2 patients have been enrolled to a newly-used dose $d$ and both of them experience DLTs, stop enrolling the third patient to $d$ and de-escalate to $d - 1$ immediately. This is ethical and sensible, as the decision would still be de-escalation if a third patient is enrolled to dose $d$ and experiences non-DLT eventually. This rule of “decision-in-advance” can accelerate the trial and make the trial conduct more ethical.

1.3.3.4 Safety Rules

For trial safety, two additional rules are applied.

- [Rule 1: Dose Exclusion] If the current dose is considered excessively toxic, i.e., $\text{Prob}\{p_d > p_T \mid \text{Data}\} > \xi$, where the threshold $\xi$ is close to 1, say 0.95, the current and all higher doses are excluded and never be used again in the remainder of the trial.

- [Rule 2: Early Stop] If the current dose is the lowest dose (first dose) and is considered excessively toxic according to Rule 1, early stop the trial for safety.

In safety Rules 1 and 2, $\text{Prob}\{p_d > p_T \mid \text{Data}\}$ is a function of the cumulative beta distribution in (1.1).

1.3.3.5 Trial Termination

The trial proceeds until any of the following conditions is satisfied:

1. If the prespecified maximum total sample size is reached;
2. If the lowest dose shows excessive toxicity according to Rule 2; In this case, the trial is early stopped and the MTD cannot be determined;
3. Optional: ad-hoc rules of maximum number of patients at a dose, denoted by $K (K < n)$:
   - If the mTPI-2 decision is “S”, to stay at the current dose, and the current dose has enrolled $K$ patients;
   - If the mTPI-2 decision is “E”, to escalate to the next higher dose, and that next higher dose has enrolled $K$ patients;
   - If the mTPI-2 decision is “D”, to de-escalate to the previous lower dose, and that previous lower dose has enrolled $K$ patients.
1.3.3.6 MTD Selection

Once all the enrolled patients complete the DLT observation and the trial is not stopped early, the mTPI-2 design applies an isotonic regression to select the MTD. Follow the steps as below.

1. Compute the isotonically transformed posterior means of DLT probabilities for all the dose levels in the following two steps.

   (a) Using the accumulated safety information about \(y_d\) and \(n_d\) for \(d = 1, \ldots, D\), compute the posterior mean and variance for all the dose levels, \(\{\tilde{p}_1, \ldots, \tilde{p}_D\}\) and \(\{v_1, \ldots, v_D\}\).

   Here in U-Design, an independent prior \(\text{beta}(0.005, 0.005)\) is used to compute the posterior mean and variance.

   (b) Compute isotonic regression estimates of the posterior mean by solving the optimization problem, minimizing \(\sum_{d=1}^{D} (\hat{p}_d - \tilde{p}_d)^2/v_d\) subject to \(\hat{p}_j \geq \hat{p}_k\), for \(j > k\). Such optimization can be done using the pooled adjacent violators algorithm (PAVA), the estimated DLT probabilities satisfying the order constraint is obtained, denoted by \(\{\hat{p}_1, \ldots, \hat{p}_D\}\).

2. Among all the tried doses for which \(\text{Prob}\{\hat{p}_d > \hat{p}_T | Data\} < \xi\) and \(\hat{p}_d \leq \hat{p}_T + \epsilon_2\), select as the estimated MTD the dose with the smallest difference \(|\hat{p}_d - \hat{p}_T|\). That is, the estimated MTD is \(d^* = \text{argmax}_d |\hat{p}_d - \hat{p}_T|\).

3. In case of a tie (i.e., two or more doses have the smallest difference),

   (a) If there is at least one dose lower the target \(\hat{p}_T\) among all the tied doses, choose the highest dose among those as the estimated MTD;

   (b) Otherwise, choose the lowest dose among the tied doses as the estimated MTD.
1.3.4 The Rolling Six Design (RSD)

The rolling six design (RSD) (Skolnik et al., 2008) extends 3+3 with the aim to reduce the occurrence of accrual suspension after enrolling each three patients and accelerate the trial conduct. It allows for accrual of two to six patients concurrently onto a dose level based on the number of patients concurrently enrolled and evaluable (# Enrolled), the number experiencing dose-limiting toxicity (DLT) (# DLTs), and the number still at risk of developing a DLT (# Pending). The rolling six is a rule-based design and all dose assignment rules for the six patients can be pretabulated (see Table 1.6).
Table 1.6: The decision table of the rolling six design.

<table>
<thead>
<tr>
<th># Enrolled</th>
<th>Observed data at dose $d$</th>
<th>Decision</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td># DLTs</td>
<td># Non-DLTs</td>
</tr>
<tr>
<td>2</td>
<td>0, 1</td>
<td>any</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>0, 1, 2</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>0, 1, 2</td>
</tr>
<tr>
<td>3</td>
<td>≥ 2</td>
<td>any</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>0, 1, 2, 3</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>0, 1, 2, 3</td>
</tr>
<tr>
<td>4</td>
<td>≥ 2</td>
<td>any</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>0, 1, 2, 3, 4</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>0, 1, 2, 3, 4</td>
</tr>
<tr>
<td>5</td>
<td>≥ 2</td>
<td>any</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>0, 1, 2, 3, 4</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>5, 6</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>0, 1, 2, 3, 4</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>6</td>
<td>≥ 2</td>
<td>any</td>
</tr>
</tbody>
</table>

NOTE. 1) This table does not take into account inevaluable patients, such as patients who drop off during the DLT observation period; 2) Escalation never occurs to a dose at which 2 or more DLTs have already occurred, because that dose level is considered excessive toxicity and should be excluded in the remaining dose finding; 3) If de-escalation occurs at the lowest dose level, then the study is early terminated.

Abbreviations: DLT, dose-limiting toxicity; MTD, maximum tolerated dose; E, escalate to next higher dose level; S, stay at the current dose level; D, de-escalate to previous lower dose level.
1.3.5 The Rolling Toxicity Probability Interval (R-TPI) Design

This section describes the rolling toxicity probability interval (R-TPI) design proposed by Guo et al. (2019). R-TPI design combines the idea of rolling accrual in rolling six design (Skolnik et al., 2008) (§1.3.4) with the model-based framework in mTPI-2 (Guo et al., 2017) (§1.3.3). Accordingly R-TPI enjoys the benefits of model-based inference and overcomes the drawback of fixed cohort size.

1.3.5.1 Notations

Consider a toxicity-driven phase I dose-finding trial. Let $p_T$ be the target DLT probability, and $p_d$ be the true and unknown DLT probabilities of dose level $d$, $d = 1, \ldots, D$, where $D$ denotes the prespecified number of dose levels to be investigated. Generally, we assume that $p_d$ is non-decreasing with dose level, i.e. $p_1 \leq p_2 \leq \cdots \leq p_D$. Assume at a given moment, dose $d$ is being used to treat enrolled patients and a total of $(n_d + m_d)$ patients have been assigned to dose $d$, among whom $n_d$ patients have known outcomes (either with or without DLT) and $m_d$ patients are still being followed without outcomes. Let $y_d$ be the number of patients (among $n_d$) with DLT, therefore $(n_d - y_d)$ without DLT. The table below describes the breakdowns.

<table>
<thead>
<tr>
<th># with DLT</th>
<th># without DLT</th>
<th># being followed and no outcomes</th>
<th>Total at dose $d$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$y_d$</td>
<td>$(n_d - y_d)$</td>
<td>$m_d$</td>
<td>$(n_d + m_d)$</td>
</tr>
</tbody>
</table>

1.3.5.2 Dose-Finding Rules and Design Algorithm

The R-TPI design consists of two sets of enrollment schemes, namely the run-in enrollment and the rolling enrollment. To begin the trial, R-TPI enrolls the first patient at the starting dose level.

Run-in Enrollment The run-in enrollment is applied to any new dose level when it is first used to treat patients during the trial. Suppose dose $d$ is decided to be the new dose level for treating patients and it has not been used at any time of the trial. R-TPI starts run-in enrollment and keeps enrolling new patients at dose $d$ until any one of two below case,

1. $n_d > 0$, i.e. there is at least one outcome at $d$,
2. $n_d = 0$ and $m_d = C$, for a pre-determined $C$ value, i.e., the first $C$ patients have not completed follow-up at $d$ and are without definitive outcomes. Here, $C$ is the maximum number of pending patients without observed outcomes allowed in the trial such that a new patient can be enrolled. For example, for the rolling six design, $C = 6$.

And then,

- in the case (1), R-TPI starts rolling enrollment (specified below).
in the case (2), R-TPI first suspends the enrollment until the first outcome at current dose $d$
and then starts the rolling enrollment (specified below).

**Rolling Enrollment** Suppose at a given moment of the trial a new patient becomes eligible for
enrollment, and the current dose used for treating patients is $d$ at which $(n_d + m_d)$ patients have been
treated. To explain the rolling enrollment, there are two more notations needed to be introduced.

- $k_d$: number of patients at dose $d$ since it most recently becomes the current dose.
  
  For example, if initially three patients are enrolled at dose level $d$, and based on their DLT
  outcomes R-TPI changes the dose level to another dose and enrolls patients at the new dose;
  however, based on the patients DLT outcomes at the new dose R-TPI changes the dose level
  again, switches back to dose $d$, and enrolls additional 3 patients. At this time $k_d = 3$.

- $D_{y_d, n_d}$: the mTPI-2 decision based on the toxicity data of $y_d$ out of $n_d$ patients experiencing
  DLTs at dose $d$, $D_{y_d, n_d} \in \{D, E, S\}$. Here, “D” stands for de-escalating to the previous
  lower dose level $d - 1$, “E” for escalating to the next higher dose level $d + 1$, and “S” for
  staying at the current dose level $d$. For the detailed mTPI-2 dose escalation rule, please refer
  to §1.3.3.2.

The dose-assignment decisions in the rolling enrollment is mainly based on the mTPI-2 decision
of current observation $D_{y_d, n_d}$, the mTPI-2 decision of the most toxic scenario where all pend-

<table>
<thead>
<tr>
<th>mTPI-2 decision for current observation $(D_{y_d, n_d})$</th>
<th>mTPI-2 decision for the most toxic scenario $(D_{y_d+m_d, n_d+m_d})$</th>
<th>mTPI-2 decision for the safest scenario $(D_{y_d, n_d+m_d})$</th>
<th>R-TPI Decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>D</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>Case 2</td>
<td>D</td>
<td>D</td>
<td>S or E</td>
</tr>
<tr>
<td>Case 3</td>
<td>S</td>
<td>S or D</td>
<td>S</td>
</tr>
<tr>
<td>Case 4</td>
<td>S</td>
<td>S or D</td>
<td>E</td>
</tr>
<tr>
<td>Case 5</td>
<td>E</td>
<td>E</td>
<td>E</td>
</tr>
<tr>
<td>Case 6</td>
<td>E</td>
<td>S or D</td>
<td>E</td>
</tr>
</tbody>
</table>

* If 3 or more continuous patients has been enrolled to the same dose ($k_d > 3$), suspend the trial to
  avoid over-enrolling patients on the current dose.

Abbreviations: E, escalate to next higher dose level; S, stay at the current dose level; D, de-escalate
to previous lower dose level.
1.3. Statistical Methods Review

1.3.5. The Rolling Toxicity Probability Interval (R-TPI) Design

ing patients experience DLTs in the future $D_{y_d+m_d,n_d+m_d}$, and the mTPI-2 decision of the safest scenario where none of pending patients experiences DLT in the future $D_{y_d,n_d+m_d}$, which can be summarized in Table 1.7. Specifically, suppose a new patient is eligible for enrollment, the detailed rolling enrollment rules are described below.

I. If $m_d = 0$, i.e., all the patients enrolled at dose level $d$ have completed their followup with definitive outcomes, assign the new patient according to $D_{y_d,n_d}$, the decision of mTPI-2 when $y_d$ out of $n_d$ patients experience DLT outcomes.

II. If $0 < m_d \leq C$, i.e., some patients are still being followed without outcomes, consider three cases:

1. If $D_{y_d,n_d}$ is $D$, consider the following two cases:
   (a) if $D_{y_d,n_d+m_d}$ is $D$, de-escalate to dose level $(d - 1)$; apply the run-in enrollment if dose $(d - 1)$ is a new dose or re-apply the rolling enrollment if it has been used before;
   (b) else, the decision is $S$ and continue patient enrollment at dose $d$.

2. If $D_{y_d,n_d}$ is $S$, consider the following two cases:
   (a) if $D_{y_d,n_d+m_d}$ is $S$, assign the new patient to $d$;
   (b) if $D_{y_d,n_d+m_d}$ is $E$,
      i. if $k_d < 3$, enroll the next patient at dose $d$;
      ii. if $k_d \geq 3$, suspend the enrollment until more patients have observed their outcomes at dose $d$. Then recalculate the $m_d$ value and re-apply I or II.

3. If $D_{y_d,n_d}$ is $E$, consider the following two cases:
   (a) if $D_{y_d+m_d,n_d+m_d}$ is $E$, escalate to dose level $(d + 1)$; apply the run-in enrollment if dose $(d + 1)$ is a new dose or re-apply the rolling enrollment if it has been used before.
   (b) else,
      i. if $k_d < 3$, enroll the next patient to dose $d$;
      ii. if $k_d \geq 3$, suspend the enrollment until more patients have observed their outcomes at dose $d$. Then recalculate the $m_d$ value and re-apply I or II.

III. If $m_d > C$, suspend the enrollment until more patients have observed outcomes at dose $d$. 
Module 1. Single-Agent Dose-Finding Designs with Toxicity Endpoint and Rolling Enrollment

1.3.5.3 Safety Rules

For trial safety, two additional rules are applied.

– [Rule 1: Dose Exclusion] If the current dose is considered excessively toxic, i.e., \( \text{Prob}\{p_d > p_T | Data\} > \xi \), where the threshold \( \xi \) is close to 1, say 0.95, the current and all higher doses are excluded and never be used again in the remainder of the trial.

– [Rule 2: Early Stop] If the current dose is the lowest dose (first dose) and is considered excessively toxic according to Rule 1, early stop the trial for safety.

Here, \( \text{Prob}\{p_d > p_T | Data\} \) is a function of the cumulative beta distribution \( \text{Beta}(\alpha_0 + y_d, \beta_0 + n_d - y_d) \). In U-Design, we use \( \alpha_0 = \beta_0 = 1 \). One thing needs to be noticed, at the time a dose is deemed unsafe and suspended, there may be some patients with pending outcomes at this dose level. Once these data are observed later, if the safety rule is no longer violated, this dose could be reopened again for further evaluation.

1.3.5.4 Trial Termination

The R-TPI design continues until any of the following conditions is satisfied:

1. If the prespecified maximum total sample size is reached;
2. If the lowest dose shows excessive toxicity according to Rule 2; In this case, the trial is early stopped and the MTD cannot be determined;
3. Optional: ad-hoc rules of maximum number of patients at a dose, denoted by \( K (K < n) \):
   - If the mTPI-2 decision is “S”, to stay at the current dose, and the current dose has enrolled \( K \) patients;
   - If the mTPI-2 decision is “E”, to escalate to the next higher dose, and that next higher dose has enrolled \( K \) patients;
   - If the mTPI-2 decision is “D”, to de-escalate to the previous lower dose, and that previous lower dose has enrolled \( K \) patients.

1.3.5.5 MTD Selection

Once all the enrolled patients complete the DLT observation and the trial is not stopped early, the R-TPI design applies an isotonic regression to select the MTD. Follow the steps as below.

1. Compute the isotonically transformed posterior means of DLT probabilities for all the dose levels in the following two steps.
   (a) Using the accumulated safety information about \( y_d \) and \( n_d \) for \( d = 1, \ldots, D \), compute
the posterior mean and variance for all the dose levels, \( \{\tilde{p}_1, \cdots, \tilde{p}_D\} \) and \( \{v_1, \cdots, v_D\} \).

Here in U-Design, an independent prior \( \text{beta}(0.005, 0.005) \) is used to compute the posterior mean and variance.

(b) Compute isotonic regression estimates of the posterior mean by solving the optimization problem, minimizing \( \sum_{d=1}^{D} (\hat{p}_d - \tilde{p}_d)^2 / v_d \) subject to \( \hat{p}_j \geq \hat{p}_k \), for \( j > k \). Such optimization can be done using the pooled adjacent violators algorithm (PAVA), the estimated DLT probabilities satisfying the order constraint is obtained, denoted by \( \{\hat{p}_1, \cdots, \hat{p}_D\} \).

2. Among all the tried doses for which \( \text{Prob}\{p_d > p_T \mid \text{Data}\} < \xi \) and \( \hat{p}_d \leq p_T + \epsilon_2 \), select as the estimated MTD the dose with the smallest difference \( |\hat{p}_d - p_T| \). That is, the estimated MTD is \( d^* = \arg\max_d |\hat{p}_d - p_T| \).

3. In case of a tie (i.e., two or more doses have the smallest difference),
   (a) If there is at least one dose lower the target \( p_T \) among all the tied doses, choose the highest dose among those as the estimated MTD;
   (b) Otherwise, choose the lowest dose among the tied doses as the estimated MTD.

1.3.5.6 R-TPI Decision Table

The R-TPI design requires users to provide the value of the target toxicity rate \( p_T \) and two small fractions, \( \epsilon_1 \) and \( \epsilon_2 \). The \( p_T \) value can be easily elicited from the trial clinician. The values of \( \epsilon_1 \) and \( \epsilon_2 \) are can be set at 0.05 as the default (Ji et al., 2010) or elicited by asking the clinician the lower and higher bound of the DLT rate that would still be considered as close to \( p_T \). Also we need to elicit the value of \( C \) to control the speed of patient accrual. With the provided values of \( p_T, \epsilon_1, \epsilon_2, \) and \( C \), one can generate the R-TPI decision table prior to the trial. Therefore, even though a model-based rolling design, R-TPI exhibits the same simplicity and transparency as rule-based methods.

We provide the decision table of up to seven patients for R-TPI with target DLT rate \( p_T \) equal to 0.3, \( \epsilon_1 = \epsilon_2 = 0.05 \), and \( C = 3 \), as an example. See Table 1.8.
Table 1.8: R-PTI Decision Table with $p_T = 0.3$, $\epsilon_1 = \epsilon_2 = 0.05$, and $C = 3$.

<table>
<thead>
<tr>
<th>Observed data at dose $d$</th>
<th>R-PTI Decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>$n_d + m_d$</td>
<td>$y_d$</td>
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<tr>
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Reference


