Steps to use BOIN App to design a phase I trial

Yanhong Zhou, Suyu Liu, Ying Yuan

1. Generate the design flow chart and decision table for dose escalation and de-escalation.

a) Click "**Trial Setting**" tab (shown in **Figure 1**), and enter design parameters (e.g., the number of doses, target toxicity probability, cohort size, the number of cohorts, ……). Users can type in the design parameters or upload using previously saved input. For each design parameter, help is accessible by clicking on . The design parameters can be conveniently saved by clicking on "Save Input" button.

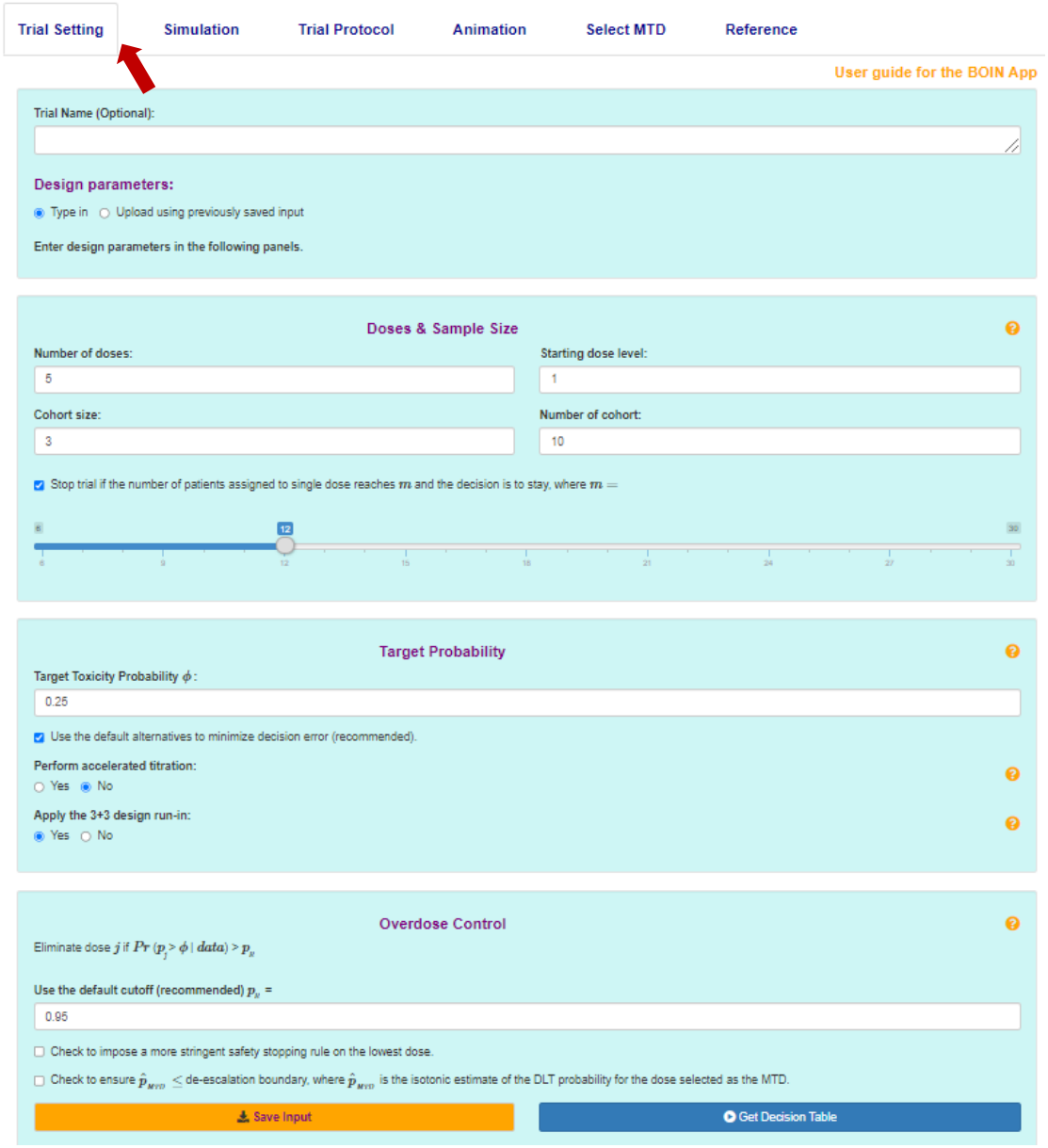


Figure 1

Remarks 1: The BOIN design has an option for accelerated titration. As indicated by the red arrow in **Figure 2.** If "**Yes**" is selected under "**Perform accelerated titration**", accelerated titration will be performed prior to treating patients according to the prespecified cohort size m, e.g., $m = 3$, as follows. Treat the first patient at the prespecified starting dose (e.g., the lowest dose) and escalate the dose in a one-patient-per-dose-level fashion until:

- **[** If the **Cap the titration up to dose level:** is the highest dose level (default) **]**: until any of the following events is observed: (i) the first instance of DLT, (ii) the second instance of moderate (grade 2) toxicity, or (iii) the highest dose level is reached. Then, treat $m - 1$ additional patients at the current dose level. Hereafter, patients are treated in cohorts of size m.

- **[** If the **Cap the titration up to dose level:** is lower than the highest dose level **]**: until either of the following events is observed: (i) the first instance of DLT, or (ii) the second instance of moderate (grade 2) toxicity. Then, treat $m - 1$ additional patients at the current dose level. Hereafter, patients are treated in cohorts of size m. In the case that the titration reaches the titration dose level upper limit without observing (i) or (ii), patients are treated in cohorts of size m from the next higher dose level.

This option is useful when the number of dose levels is large (e.g., > 6) and low dose levels are believed to be safe. It accelerates dose escalation and reduces the sample size. The tradeoff is that if the true toxicity probabilities of low dose levels are relatively high, using accelerated titration slightly increases the chance of overdosing patients.

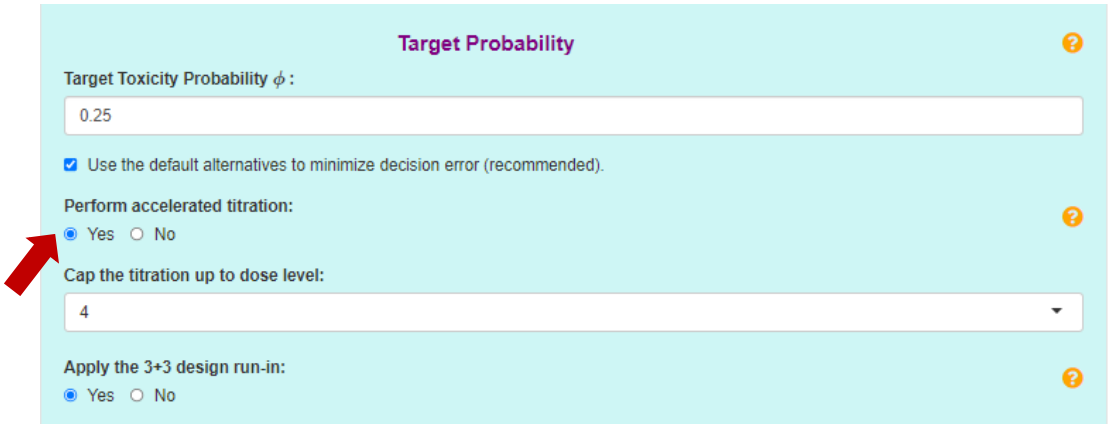


Figure 2

Remarks 2: The BOIN design has an option to impose 3+3 design rule when the number of treated patients at the current dose is 3 or 6 (available and appropriate only when the target DLT rate is 0.25). As shown in **Figure 3**, if "**Yes**" is selected under "**Apply the 3+3 design run-in**", the 3+3 design rules will kick in. That is, escalate the dose if 0/3, 0/6 or 1/6 DLT, stay at the current dose if 1/3 DLT, and de-escalate the dose if $\geq$ 2/3 or 2/6 DLTs. With this option, the resulting BOIN design (with the 3+3

design run-in) is more compatible with the conventional approach, but still advantageous because it (1) provides coherent decision rule when the number of patients treated at the current dose is other than 3 or 6; (2) allows treating more than 6 patients at the MTD to obtain a better estimate of its toxicity profile; (3) yields higher accuracy to identify the MTD because of using all data to estimate and select the MTD at the end of the trial.

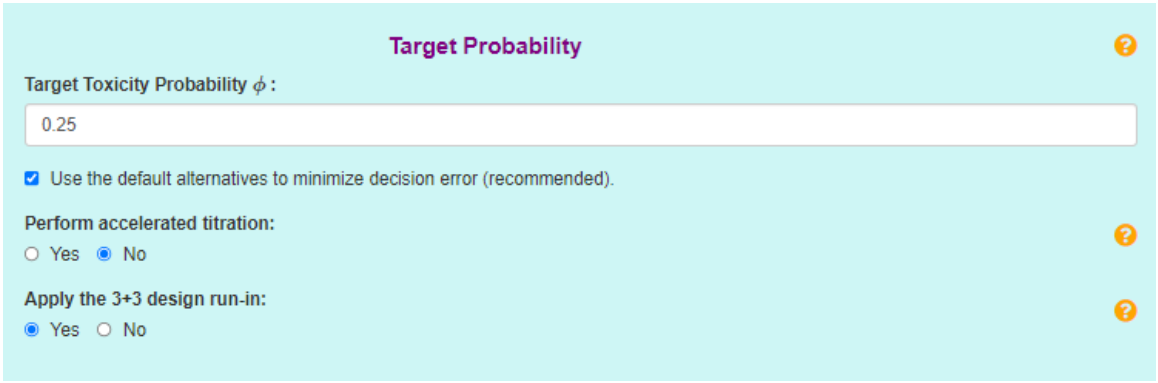


Figure 3

Remarks 3: The BOIN design has a built-in stopping rule: stop the trial if the lowest dose is eliminated due to toxicity. In this case, no dose should be selected as the MTD. The rule to eliminate a dose is specified in the "**Overdose Control**" Panel (**Figure 4**). For some applications, investigators may prefer a stricter stopping rule for extra safety when the lowest dose is possibly overly toxic. As shown below, checking the "**Check the box to impose a more stringent safety stopping rule**" imposes the following stronger stopping rule:

> Stop the trial if (1) the number of patients treated at the lowest dose > 3, and (2) $\Pr(p_1 > \phi) > P_E - \delta$, where p_1 is the true toxicity rate of the lowest dose (i.e., dose level 1), and δ is a small positive offset (between 0 and 0.1) subtracted from the cutoff probability.

This rule says that if the lowest dose exceeds a certain safety threshold, we stop the trial for safety. A larger value of δ leads to a more stringent stopping rule. The default value of $\delta = 0.05$ generally works well, but users can calibrate the value of δ to obtain desired operating characteristics. In practice, δ is rarely greater than 0.1. Note that as a trade-off, the stricter stopping rule will decrease the MTD selection percentage when the lowest dose actually is the true MTD.

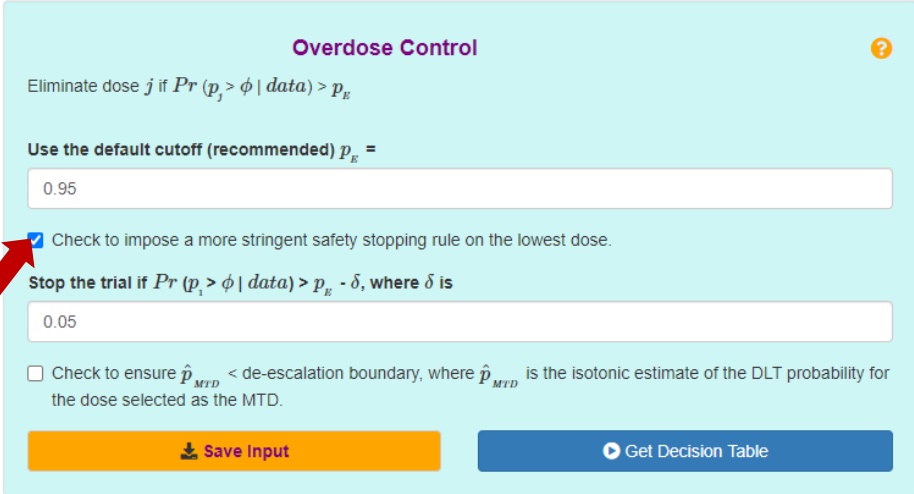


Figure 4

Remarks 4: starting from version 2.4.0.0, the BOIN design provides an option for users to impose the condition: the selected MTD should have an isotonic estimate of toxicity probability less than de-escalation boundary. As shown in **Figure 5**, checking the "**Check to ensure $\hat{p}_{MTD}$ < de-escalation boundary, where $\hat{p}_{MTD}$ tis the isotonic estimate of the DLT probability for the dose selected as the MTD**" triggers the option. This will improve safety, but at a slight sacrifice of selection percentage.

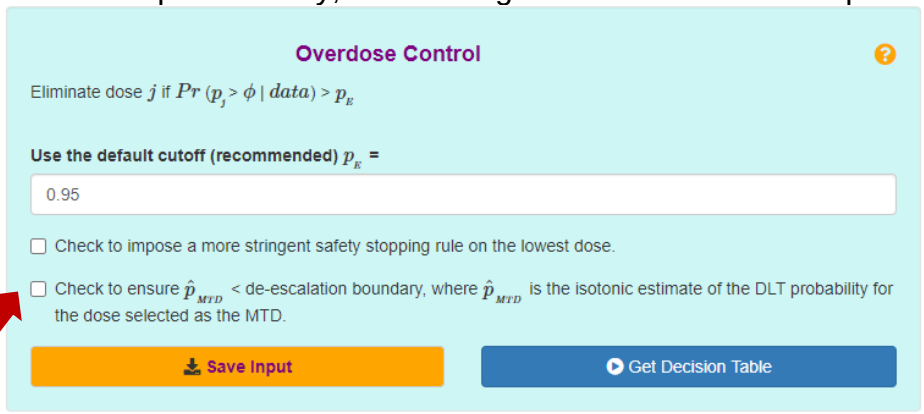


Figure 5

b) Click "**Get Flow Chart and Decision Table**" button at the bottom of "**Trial Setting**" tab to generate design flow chart and decision table for dose escalation and de-escalation (**Figure 6**). Current input can be saved by clicking on the "**Save Input**" button.

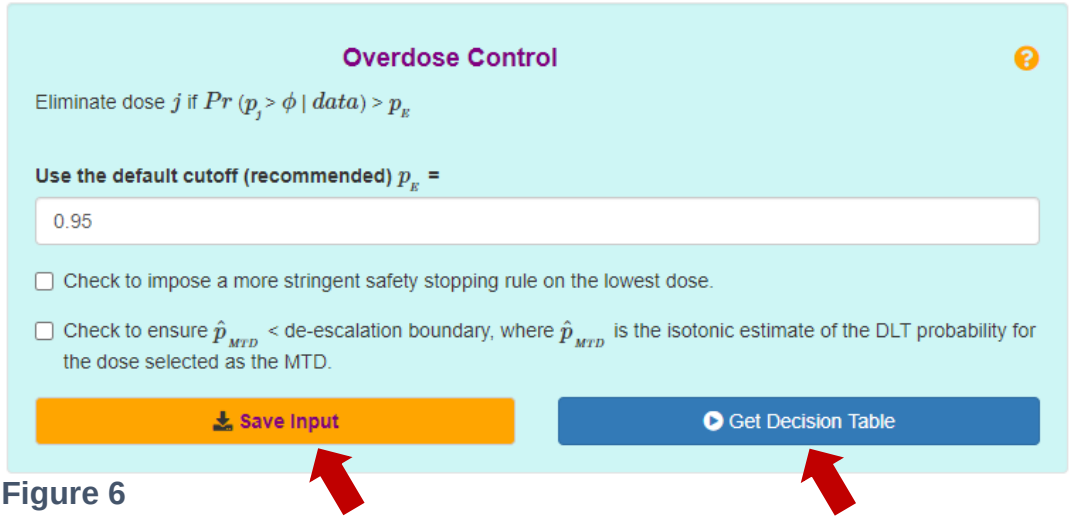


Figure 6

In the output panel, the design flow chart is available under "**Design Flow Chart**" tab (**Figure 7**); and the escalation/de-escalation decision table is available under "**Decision Table**" tab (**Figure 8**). *The Decision Table is all we need to run the trial* and conduct dose escalation and de-escalation.

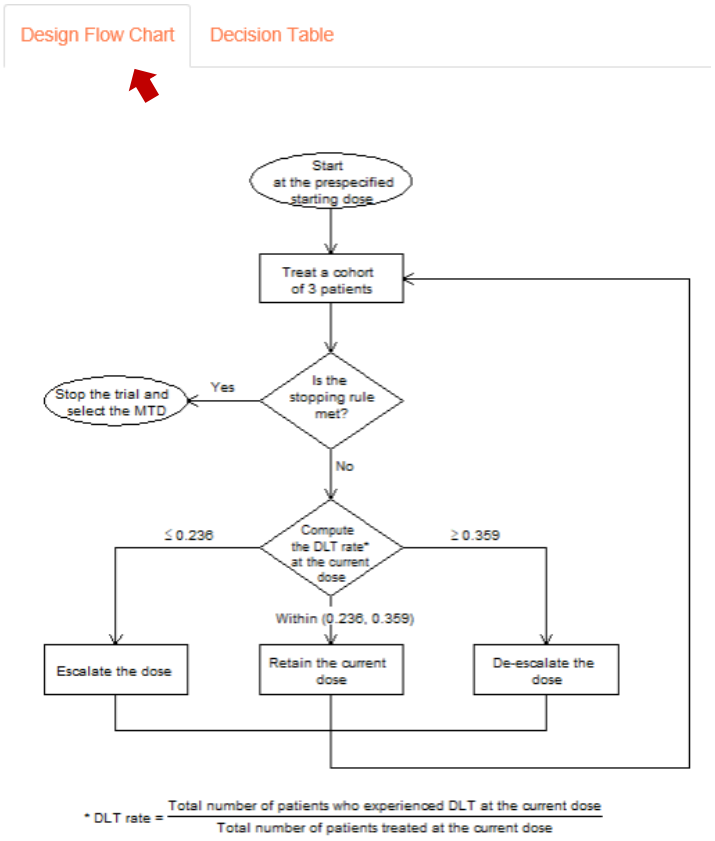


Figure 7

Design Flow Chart | Decision Table

Table 1: Dose escalation/de-escalation rule.

Copy CSV Print

	1	2	3	4	5	6	7	8	9	10	11	12
Number of patients treated	1	2	3	4	5	6	7	8	9	10	11	12
Escalate if # of DLT <=	0	0	0	0	1	1	1	1	2	2	2	2
Deescalate if # of DLT >=	1	1	2	2	2	3	3	3	4	4	4	5
Eliminate if # of DLT >=	NA	NA	3	3	4	4	5	5	5	6	6	7

Figure 8

2. Obtain operating characteristics of the design.

a) Choose either "**Type in**" or "**Upload scenario file**" method to enter simulation scenarios.

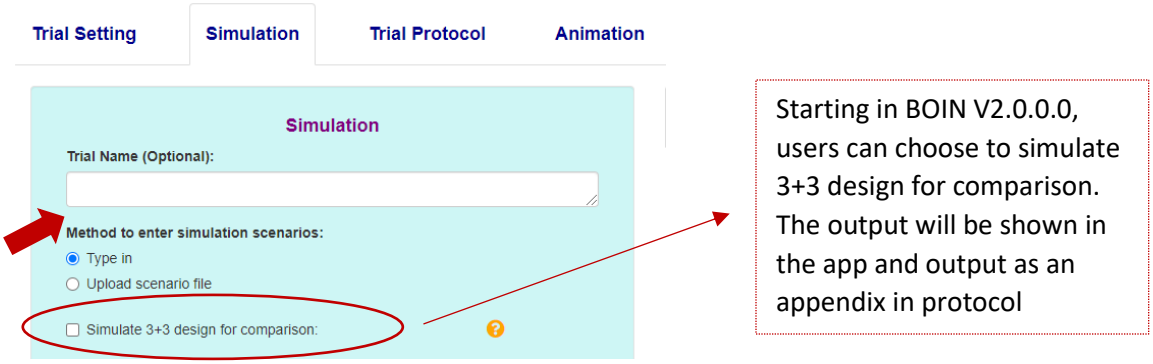


Figure 9

If "**Type in**" is selected, manually type in true toxicity probability of each dose level for each scenario. The app, by default, provides four randomly generated scenarios. To add a new scenario, click "**Add a Scenario**"; to remove an existing scenario, click "**Remove a Scenario**"; to save entered scenarios, click "**Save Scenarios**".

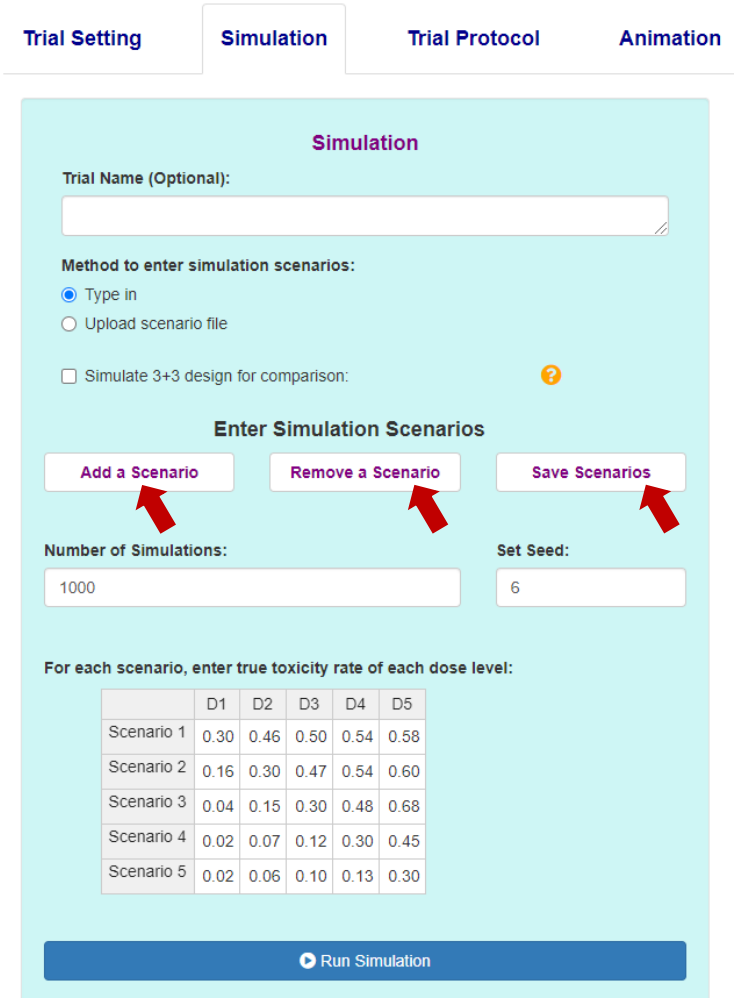


Figure 10

If “**Upload scenario file**” is selected, upload scenarios using the template downloadable through “**csv file template**”. Scenarios uploaded can be viewed by clicking the “**View uploaded Scenarios**” button.

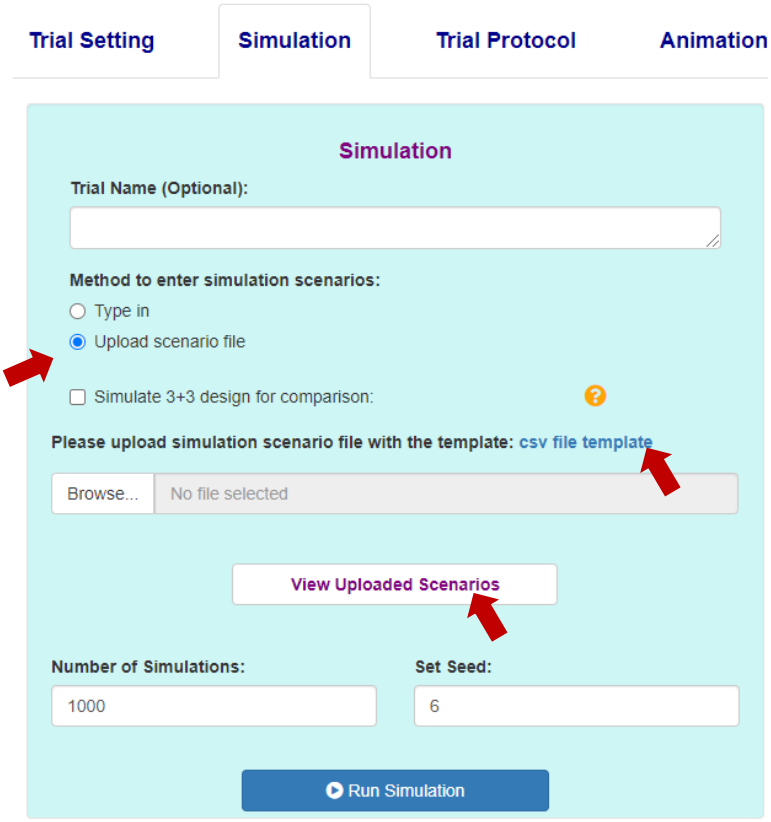


Figure 11

b). For “Type in” method, specify the desirable number of simulations, and click “**Run Simulation**”.

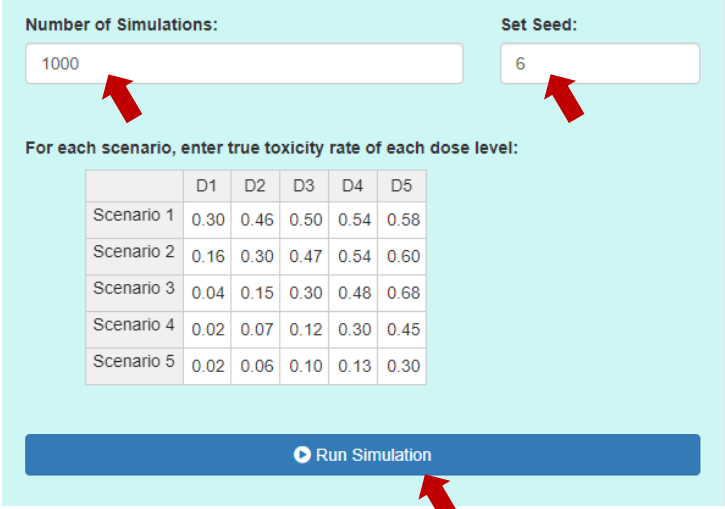
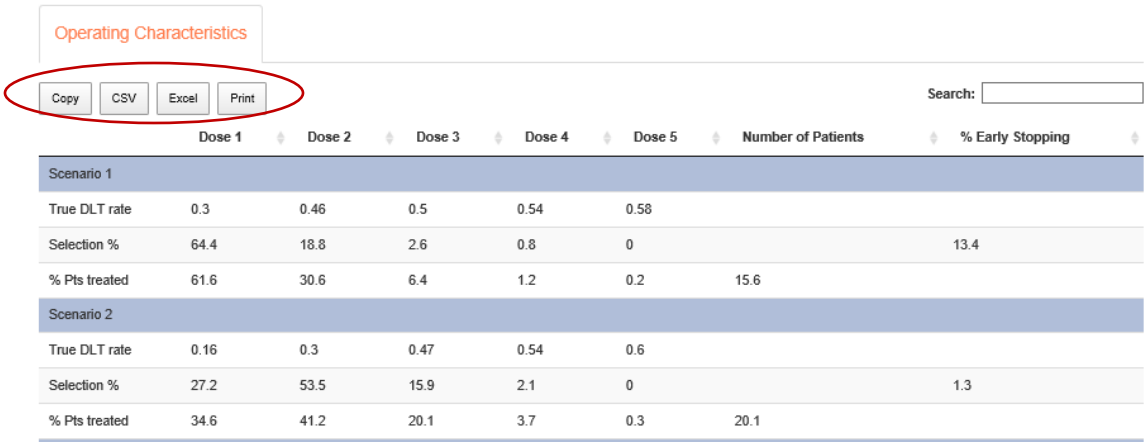


Figure 12

The simulation results will appear in the output panel under the "**Operating Characteristics**" tab. Users can copy the results or download it in different formats highlighted by the red oval below.



	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Number of Patients	% Early Stopping
Scenario 1							
True DLT rate	0.3	0.46	0.5	0.54	0.58		
Selection %	64.4	18.8	2.6	0.8	0		13.4
% Pts treated	61.6	30.6	6.4	1.2	0.2	15.6	
Scenario 2							
True DLT rate	0.16	0.3	0.47	0.54	0.6		
Selection %	27.2	53.5	15.9	2.1	0		1.3
% Pts treated	34.6	41.2	20.1	3.7	0.3	20.1	

Figure 13

3. Generate trial design protocol

After completing the simulation, the protocol template can be downloaded under the "**Trial Protocol**" Tab. The protocol template is available in both English and Chinese. For each language, we provide an html template and a word template. Depending on user's version of Word, one format may be preferable than the other. For the Word version, users may need to download Figure 1 (as shown within the red dashed rectangle in **Figure *14***) separately and paste it into the Word version.

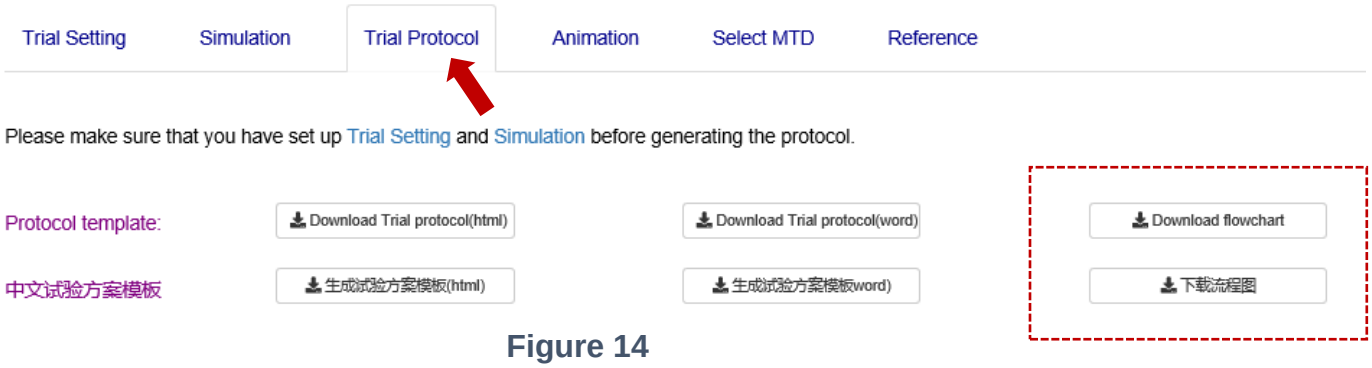


Figure 14

4. Animation

To better understand the simulation process behind the scene, users can choose to view the animation under "**Animation**" tab.

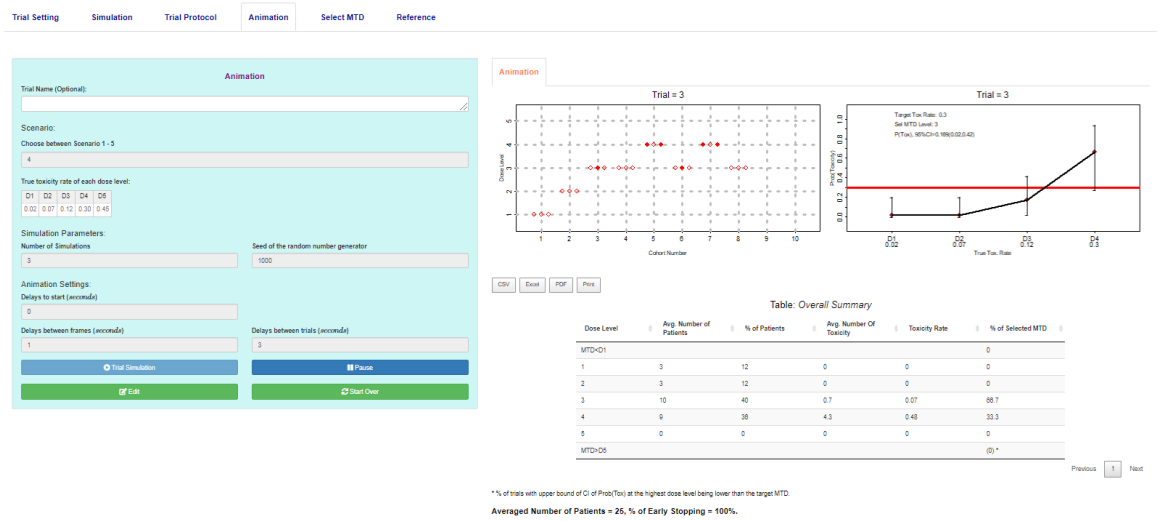


Figure 15

5. Select MTD

After the trial completes, go to the "**Select MTD**" tab, where users will be asked to enter trial parameters under "Trial Setting" first, and then enter the trial data. After that, click the "**Estimate the MTD**" button. An example is shown in Figure 14, where the selected MTD and isotonic estimates for all doses used to treat patients are shown. A PDF report is also available for download by clicking "**Download MTD Report (PDF)".**

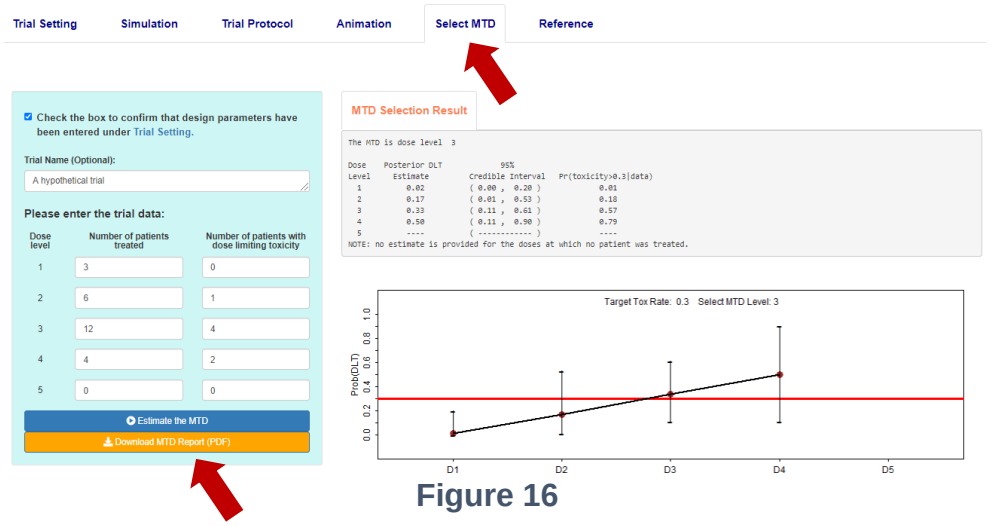


Figure 16

References

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.

Yuan Y., Hess K.R., Hilsenbeck S.G. and Gilbert M.R. (2016) Bayesian Optimal Interval Design: A Simple and Well-performing Design for Phase I Oncology Trials, *Clinical Cancer Research* , **22** , 4291-4301.

Zhou, H., Yuan, Y., & Nie, L. (2018). Accuracy, safety, and reliability of novel phase I trial designs. *Clinical Cancer Research*, 24(18), 4357-4364.

Zhou, Y., Lin, R., Kuo, Y. W., Lee, J. J., & Yuan, Y. (2021). BOIN Suite: A Software Platform to Design and Implement Novel Early-Phase Clinical Trials. *JCO Clinical Cancer Informatics*, *5*, 91-101.