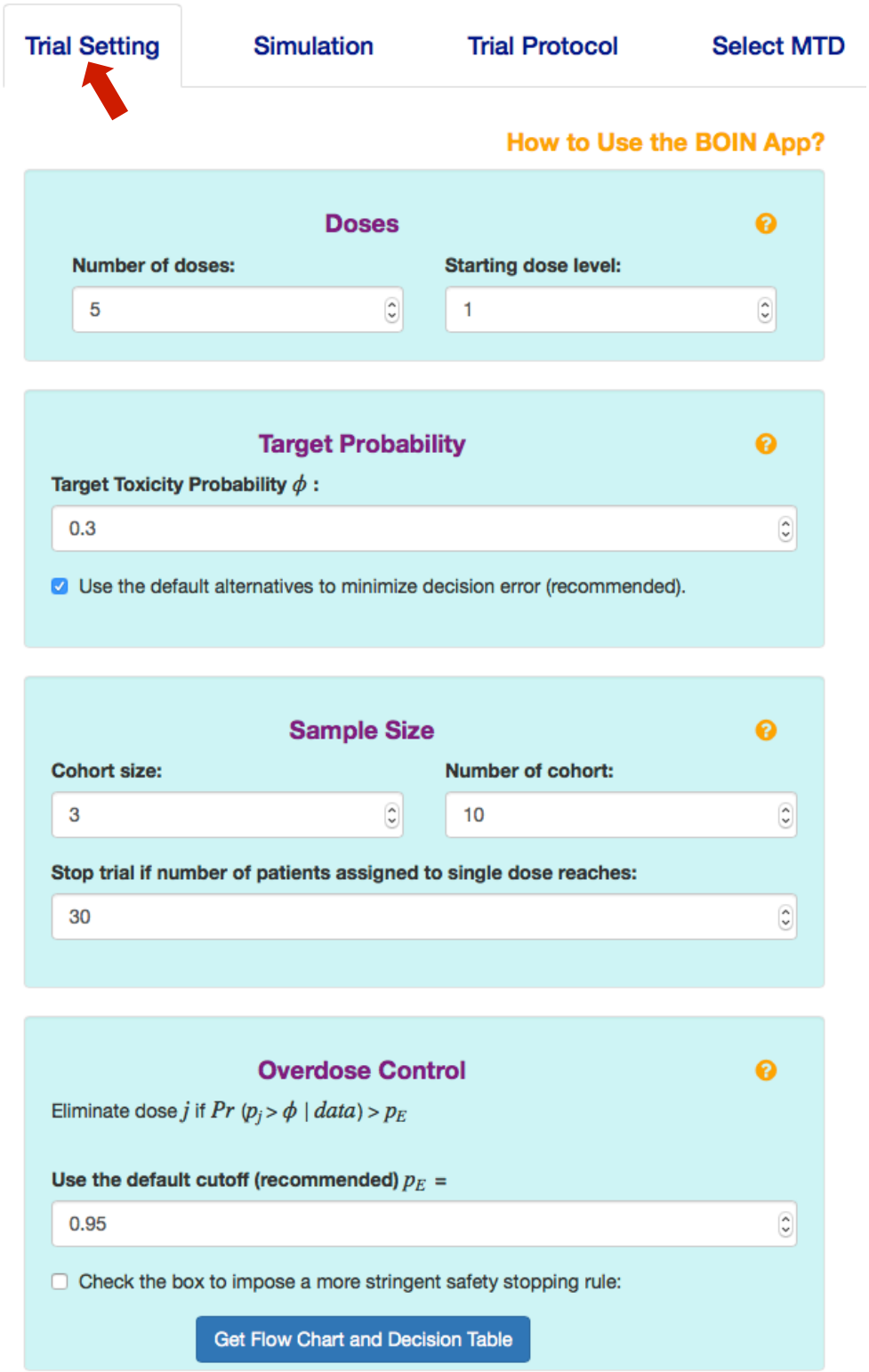
Steps to use BOIN App to design a phase I trial

Ying Yuan, Suyu Liu and Yanhong Zhou

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

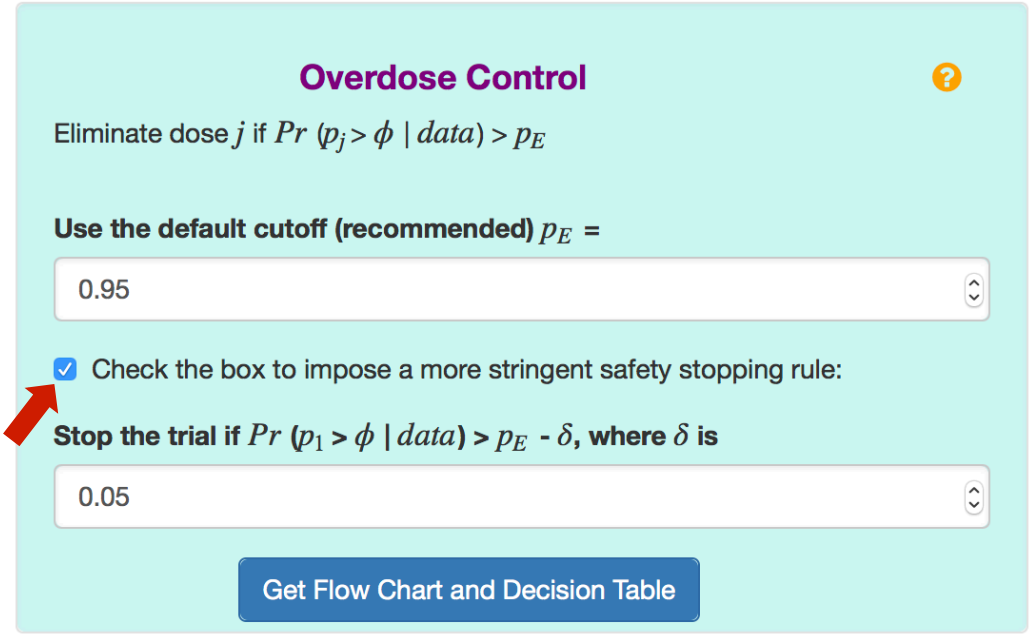
   a) Click "**Trial Setting**" tab, and enter design parameters (e.g., the number of doses, target toxicity rate, cohort size, the number of cohorts, ……). For each design parameter, help is accessible by clicking on .



Remarks: 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. 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:

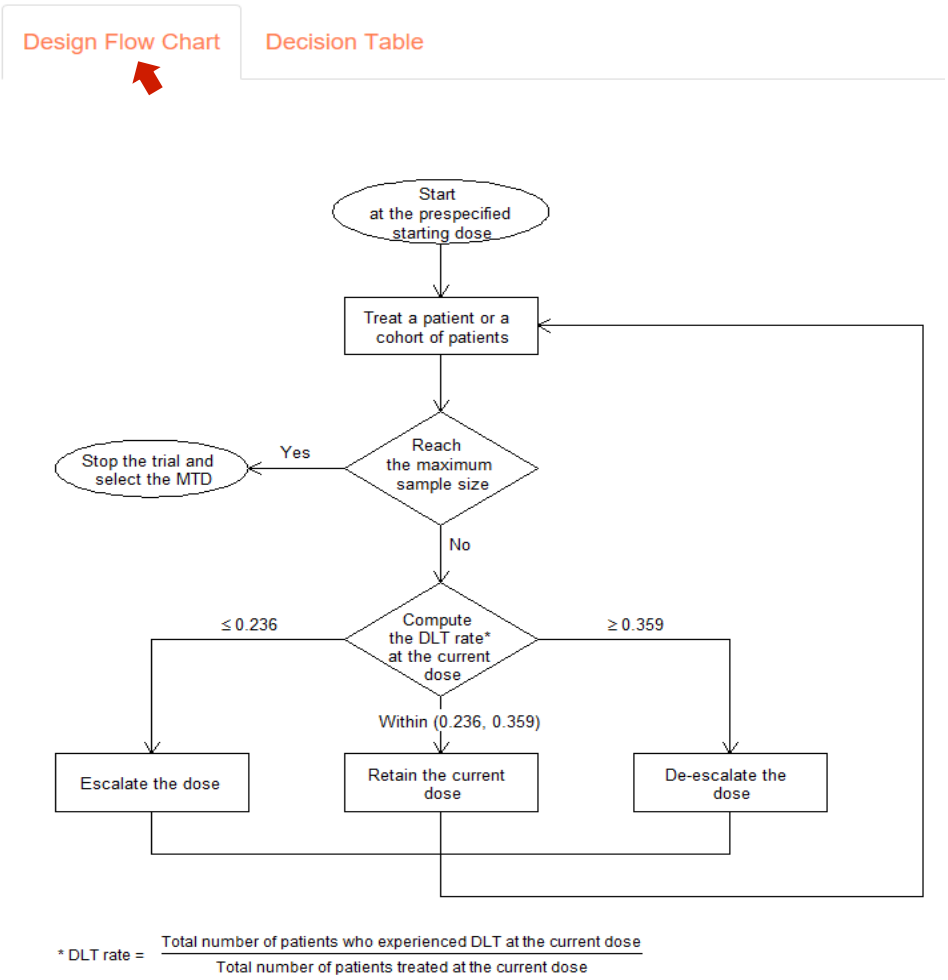
> Stop the trial if (1) the number of patients treated at the lowest dose > 3, and (2) $\Pr(p_1 > \phi) > P_E - \delta$, where p_1 is the true toxicity rate of the lowest dose (i.e., dose level 1), and δ is a small positive offset (between 0 and 0.1) subtracted from the cutoff probability.

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.



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.

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



Design Flow Chart | Decision Table

Table 1: Dose escalation/de-escalation rule.

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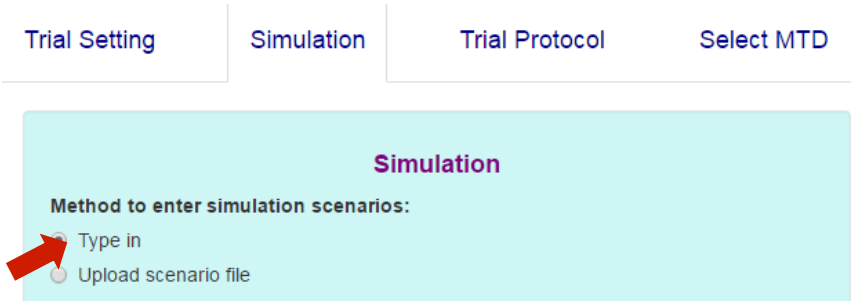
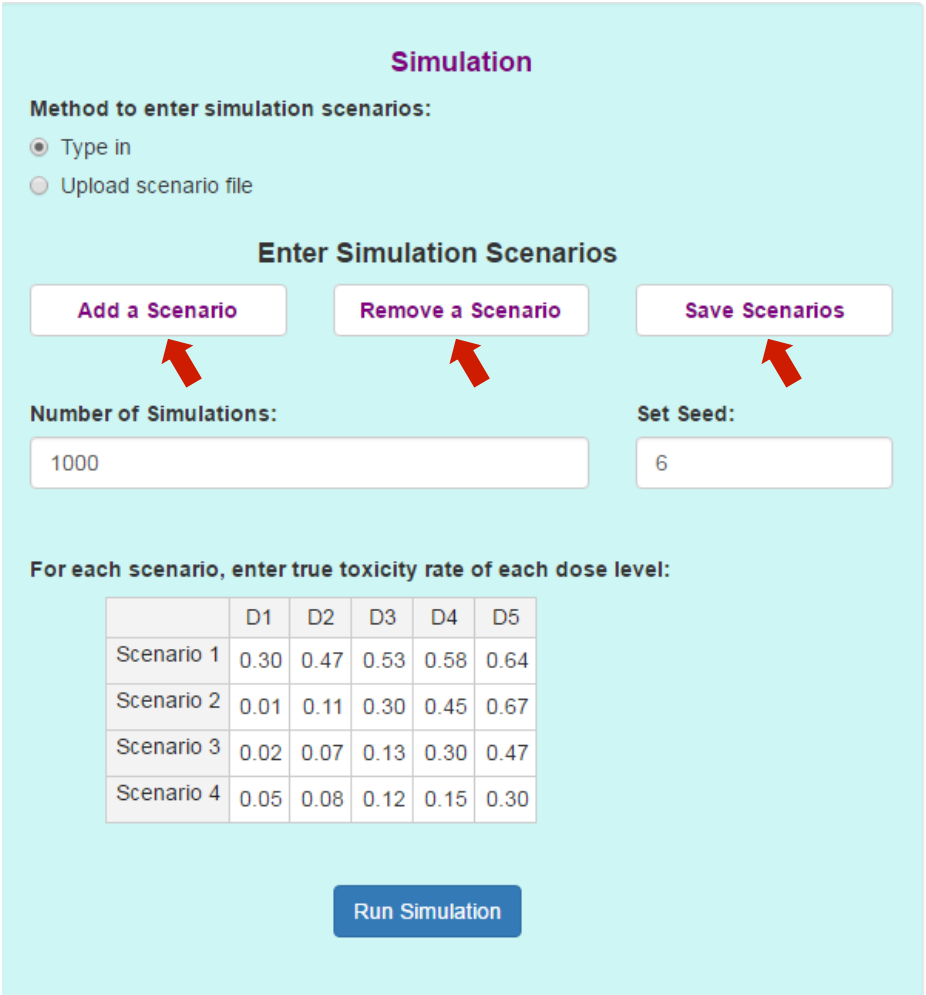
	1	2	3	4	5	6	7	8	9	10	11	12
Number of patients treated	1	2	3	4	5	6	7	8	9	10	11	12
Escalate if # of DLT <=	0	0	0	0	1	1	1	1	2	2	2	2
Deescalate if # of DLT >=	1	1	2	2	2	3	3	3	4	4	4	5
Eliminate if # of DLT >=	NA	NA	3	3	4	4	5	5	5	6	6	7

2. Obtain operating characteristics of the design.

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

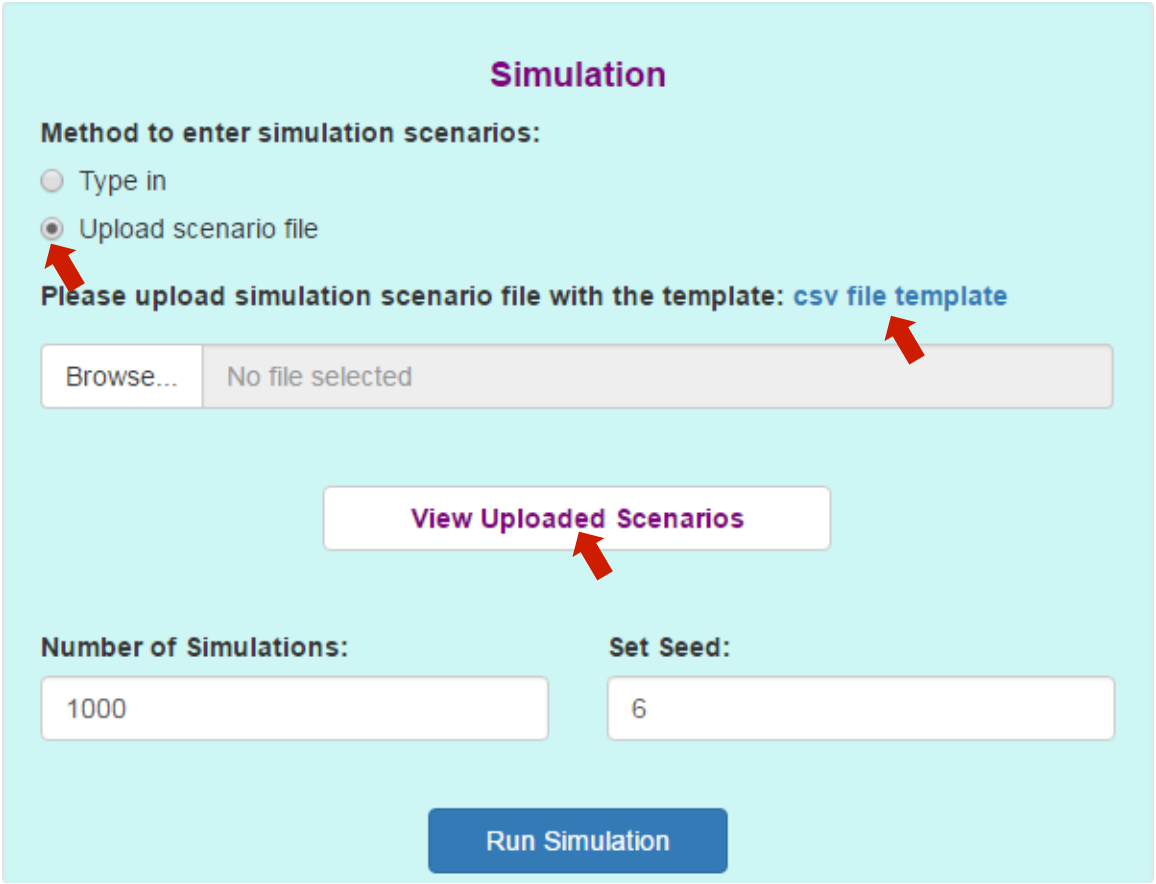


   If "**Type in**" is selected, manually type in true toxicity probability of each dose level for each scenario. The app, by default, provides four randomly generated scenarios. To add a new scenario, click "**Add a Scenario**"; to remove an existing scenario, click "**Remove a Scenario**"; to save entered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

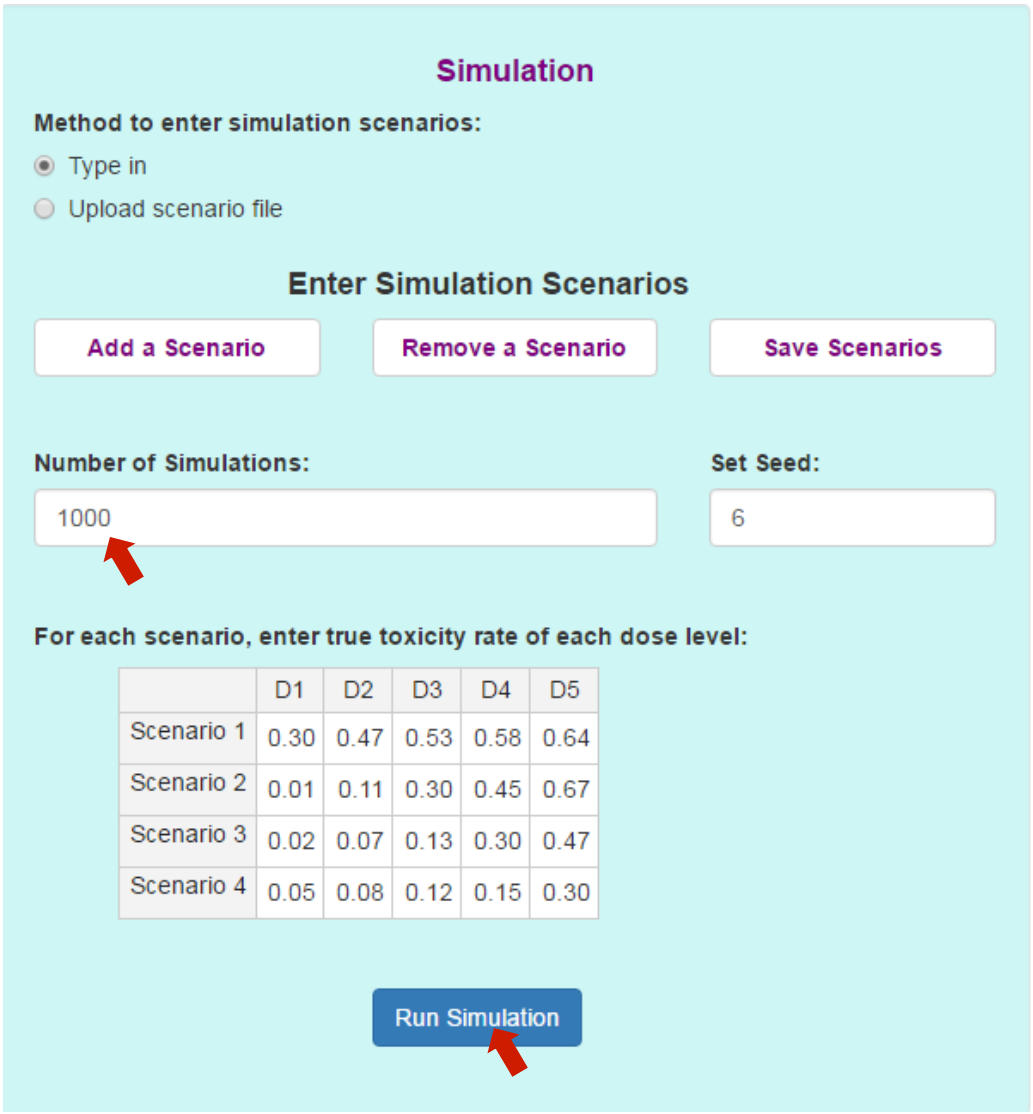


	D1	D2	D3	D4	D5
Scenario 1	0.30	0.47	0.53	0.58	0.64
Scenario 2	0.01	0.11	0.30	0.45	0.67
Scenario 3	0.02	0.07	0.13	0.30	0.47
Scenario 4	0.05	0.08	0.12	0.15	0.30

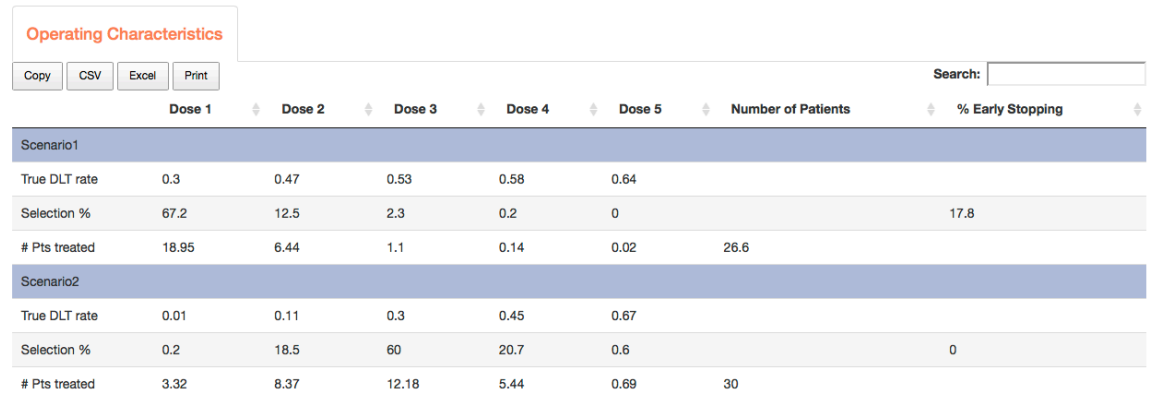
If “**Upload scenario file**” is selected, upload scenarios using the template downloadable through “**csv file template**”. Scenarios uploaded can be viewed by clicking the “**View uploaded Scenarios**” button.



b). Specify the desirable number of simulations, and click “**Run Simulation**”.



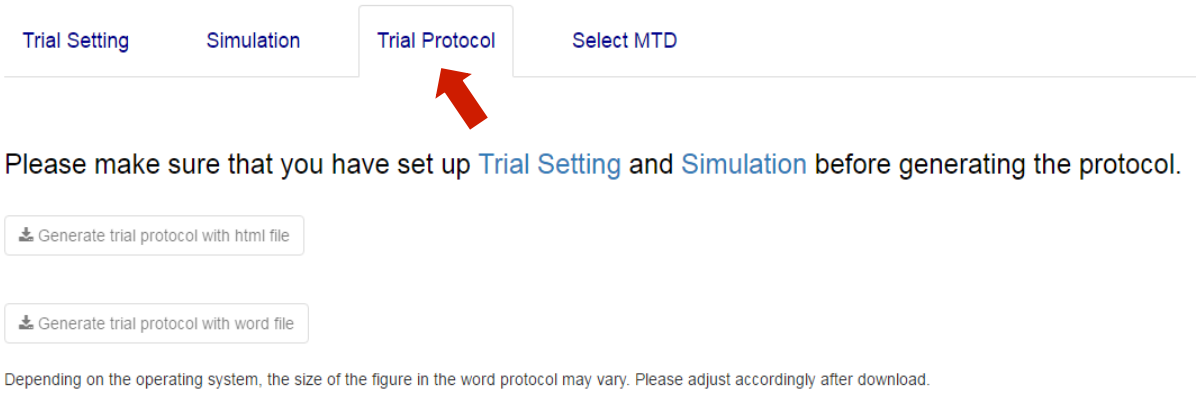
The simulation results will appear in the output panel under the “**Operating Characteristics**” tab.



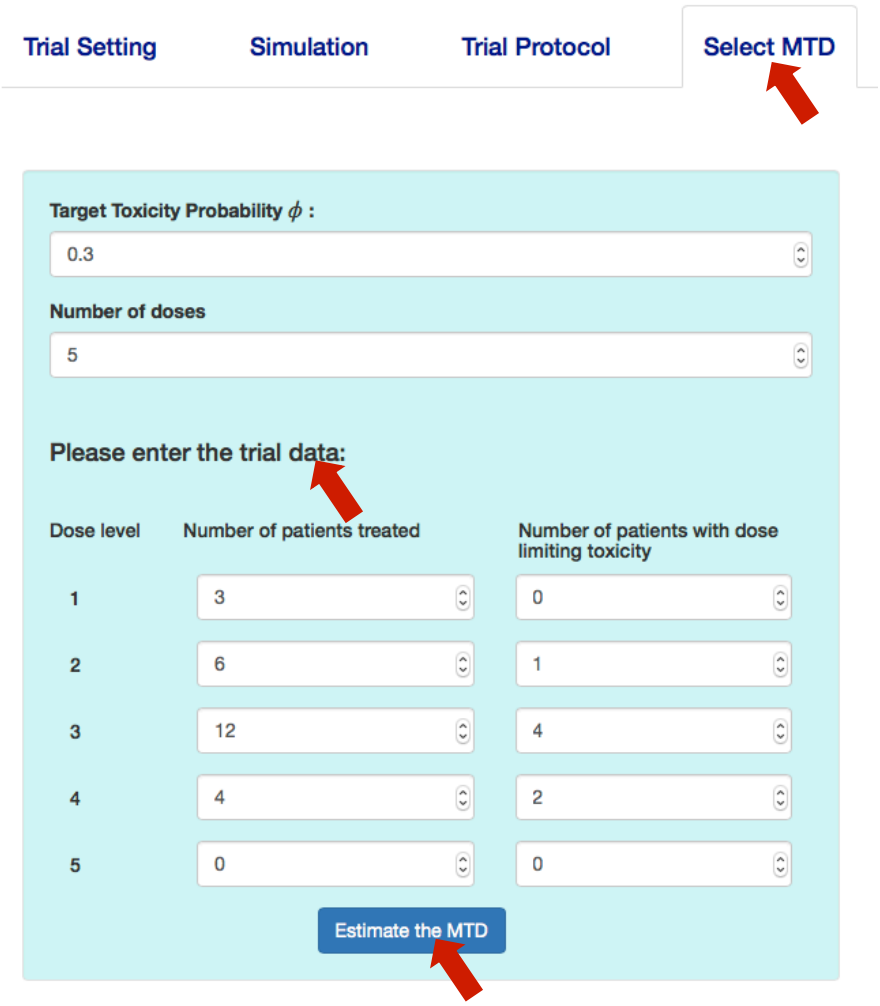
	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Number of Patients	% Early Stopping
Scenario1							
True DLT rate	0.3	0.47	0.53	0.58	0.64		
Selection %	67.2	12.5	2.3	0.2	0		17.8
# Pts treated	18.95	6.44	1.1	0.14	0.02	26.6	
Scenario2							
True DLT rate	0.01	0.11	0.3	0.45	0.67		
Selection %	0.2	18.5	60	20.7	0.6		0
# Pts treated	3.32	8.37	12.18	5.44	0.69	30	

3. Generate trial design protocol

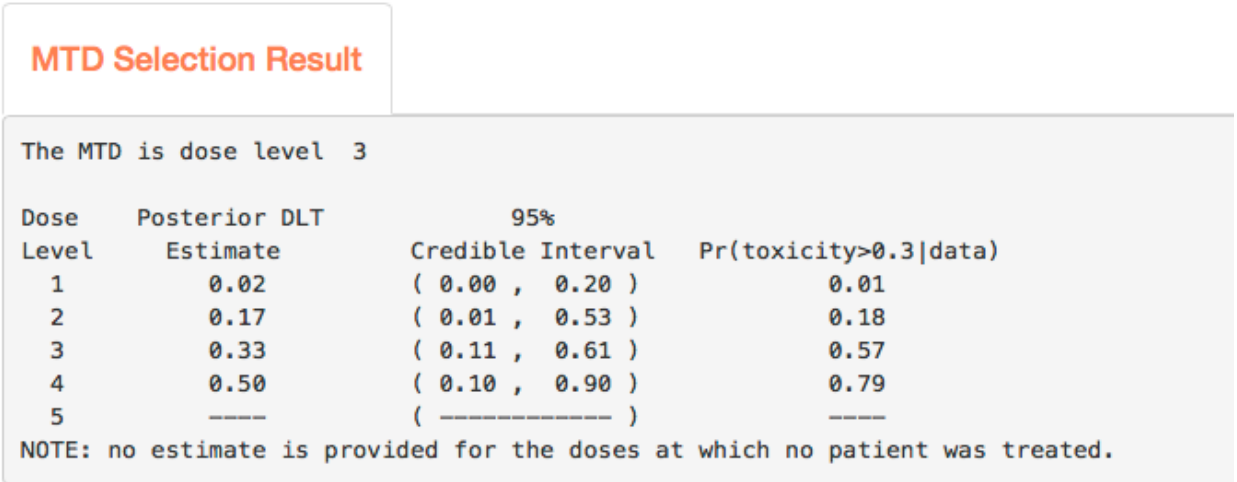
   After completing the simulation, the protocol template can be downloaded under the "**Trial Protocol**" Tab. The protocol template is available as an html file or word file. Depending on user's version of Word, one format may be preferable than the other.



4. After the trial is completed, click the "**Select MTD**" tab, enter the trial data and then click the "**Estimate the MTD**" button. An example is shown below.



The recommend MTD will appear on the output panel:



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.