Steps to use BOIN App to design a phase I drug combination trial

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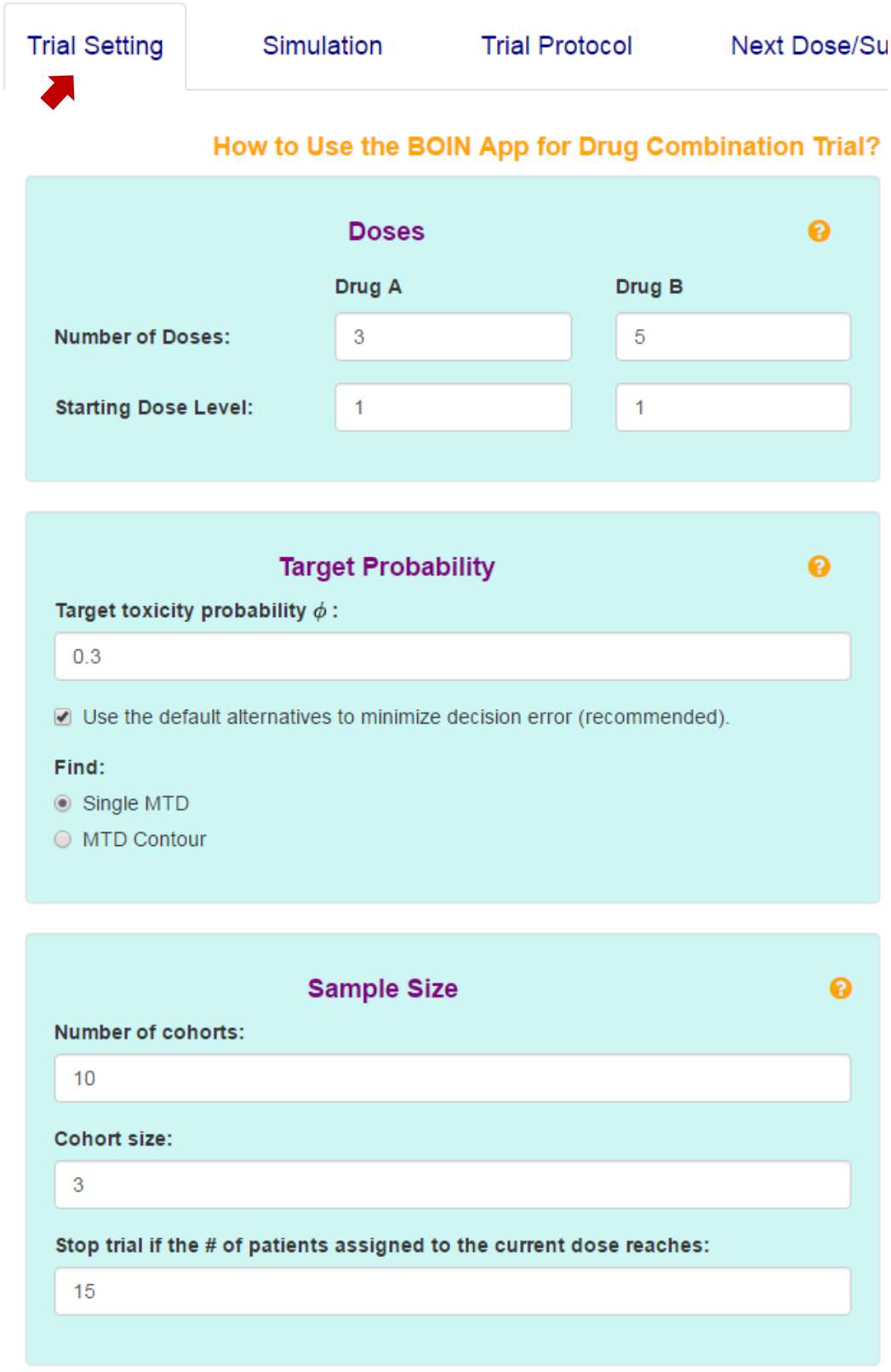
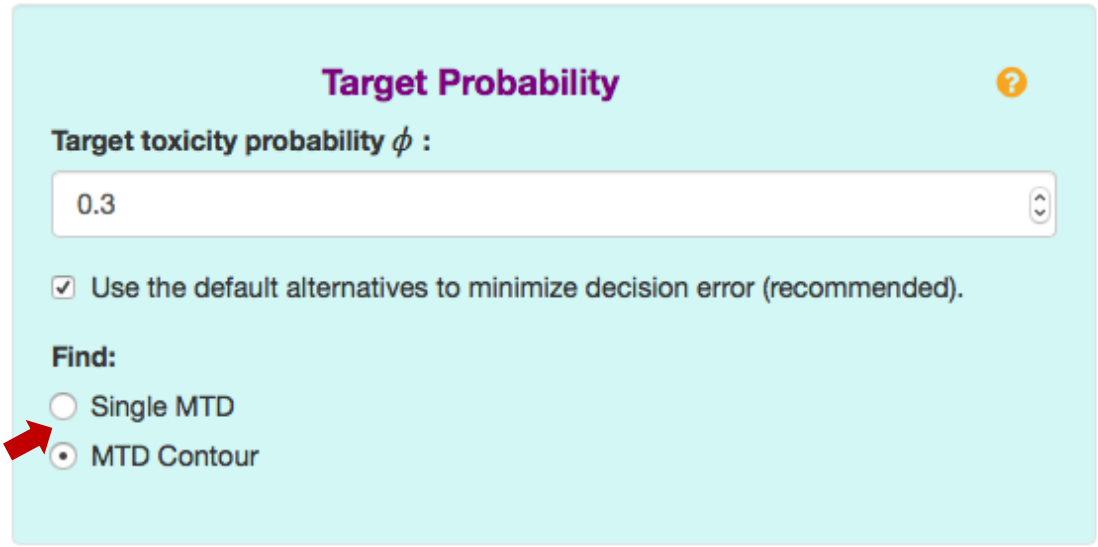
1. Generate the design flow chart and decision table
   a) Click "Trial Setting" tab, and enter design parameters (e.g., the number of doses for each drug, target toxicity rate, cohort size, the number of cohorts, etc.). For each design parameter, help is accessible by clicking on .

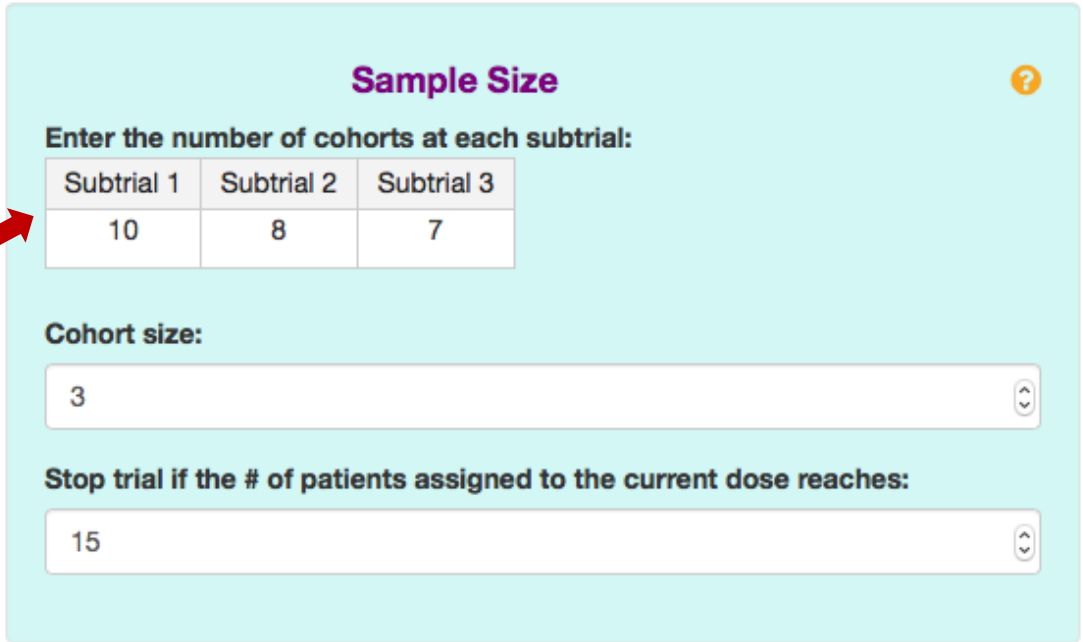


***Remarks*:**

One important design parameter is to choose the objective of the combination trial: to find a single MTD or the MTD contour (i.e., multiple MTDs). When the objective is to find the single MTD, the BOIN combination trial design will be used; when the objective is to find the MTD contour, the waterfall design will be used.



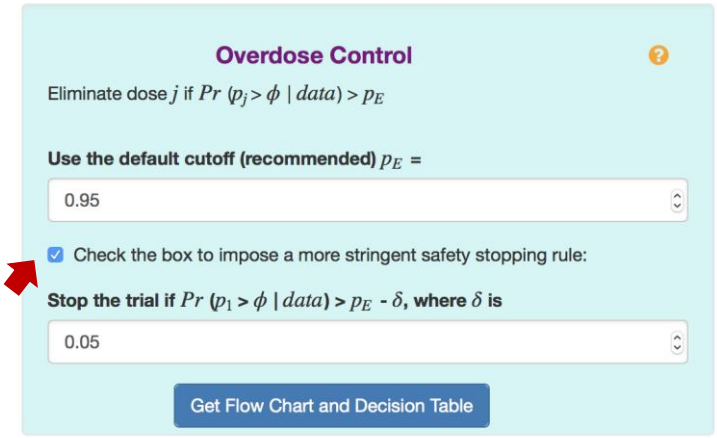
As the waterfall design divides the drug combination matrix into several subtrials, if the "MTD contour" is selected, users will need to specify the sample size for each subtrial. In generally, the first subtrial should have the largest sample size because it contains the largest number of doses.



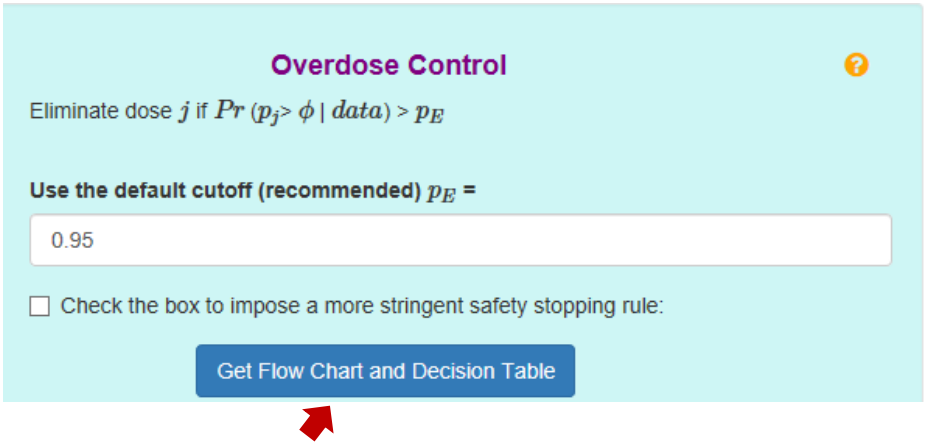
The BOIN design has a built-in stopping rule: stop the trial if the lowest dose is eliminated due to toxicity. In this case, no dose should be selected as the MTD. The rule to eliminate a dose is specified in the "**Overdose Control**" panel. For some applications, investigators may prefer a stricter 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 under "**Overdose Control**" 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.*

i. When the design aims to find a **Single MTD**, only the flowchart of trial conduct using BOIN design is shown.

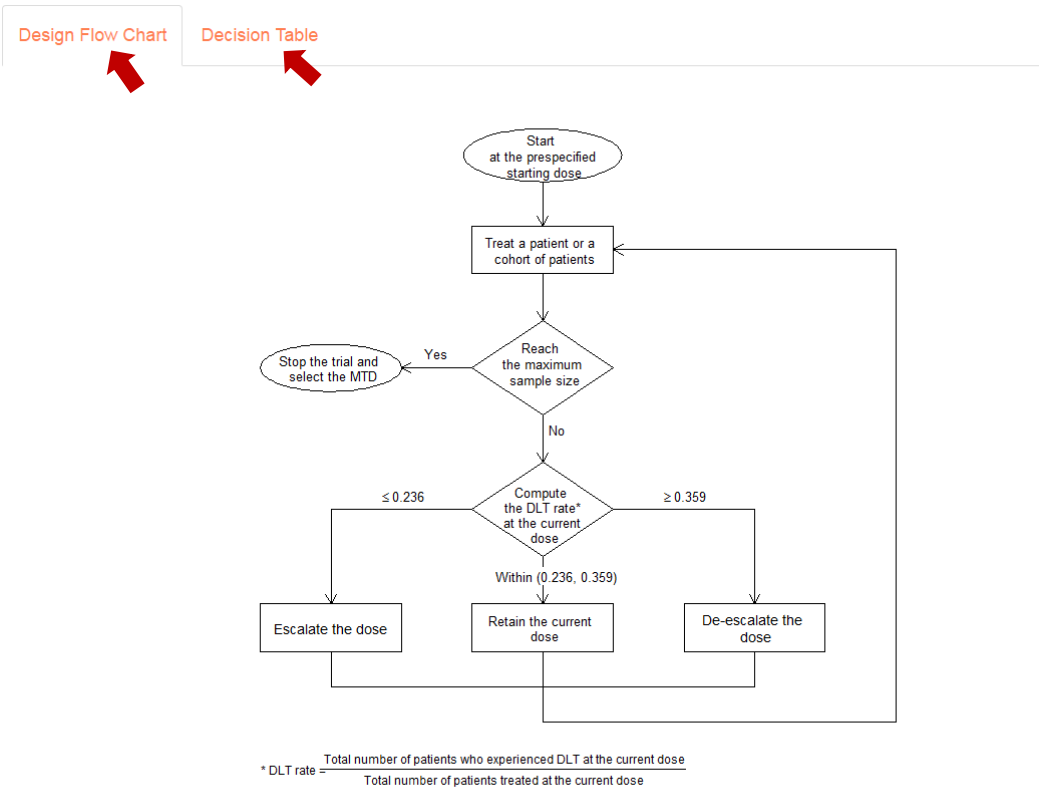


Figure 1. Flowchart for a trial conduct using the BOIN design

ii. When the design aims to find **MTD Contour**, both the flowchart of a subtrial using the BOIN design and the diagram of the waterfall design are shown.

Figure 1. Illustration of the waterfall design for a 3 x 5 combination trial

Note: The doses in the rectangle form a subtrial, and the asterisk denotes the candidate MTD. As shown in panel (a), the trial starts by conducting the first subtrial with the starting dose (1,1). After the first subtrial identifies (3,2) as the candidate MTD, conduct the second subtrial with the starting dose (2,3) (see panel (b)). After the second subtrial identifies (2,4) as the candidate MTD, conduct the third subtrial with the starting dose (1,5) (see panel (c)). After all the subtrials are completed, select the MTD contour based on the data from all the subtrials, as shown in panel (d).

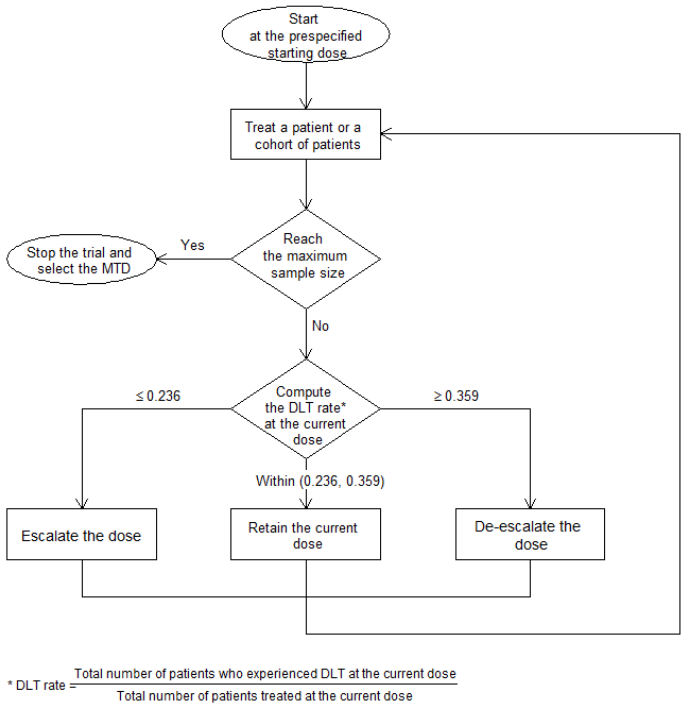
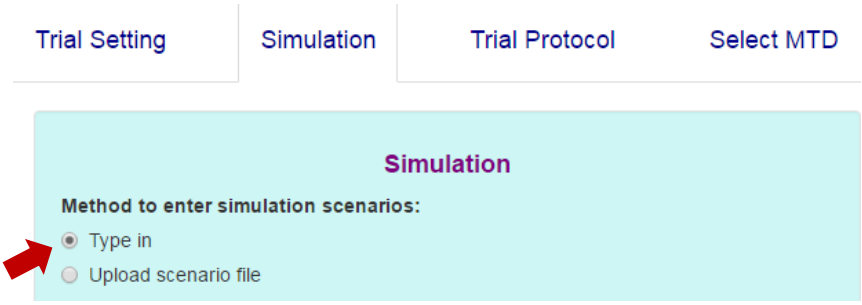


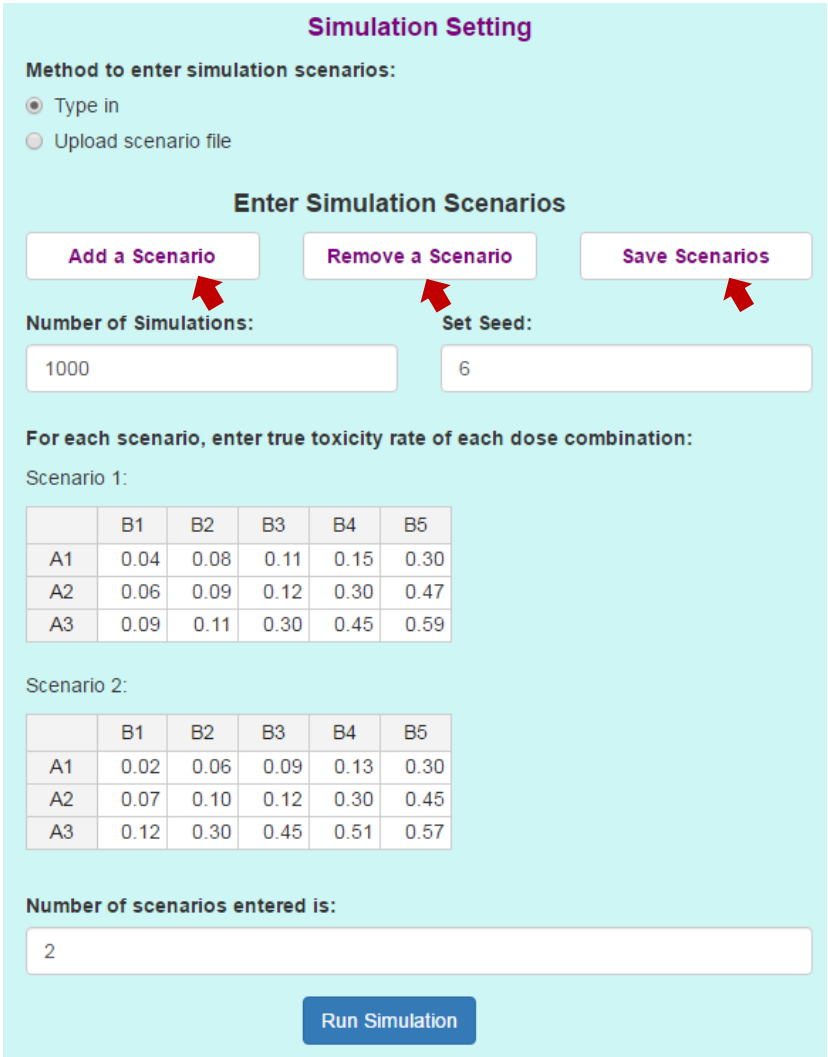
Figure 2. Flowchart for a subtrial conduct using the BOIN design

2. Obtain operating characteristics of the design

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



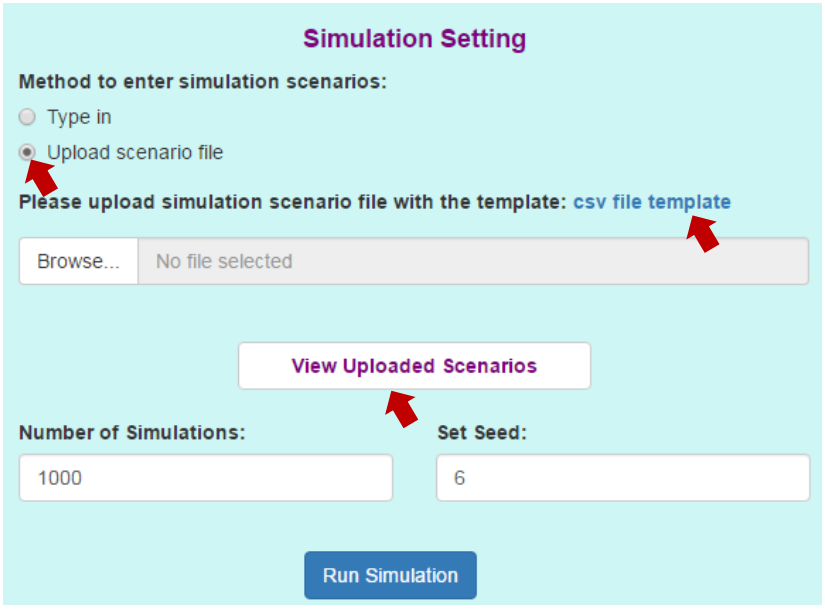
If "**Type in**" is selected, manually type in true toxicity probability of each dose combination for each scenario. The app, by default, provides four randomly generated scenarios (only two shown below). To add a new scenario, click "**Add a Scenario**"; to remove an existing scenario, click "**Remove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



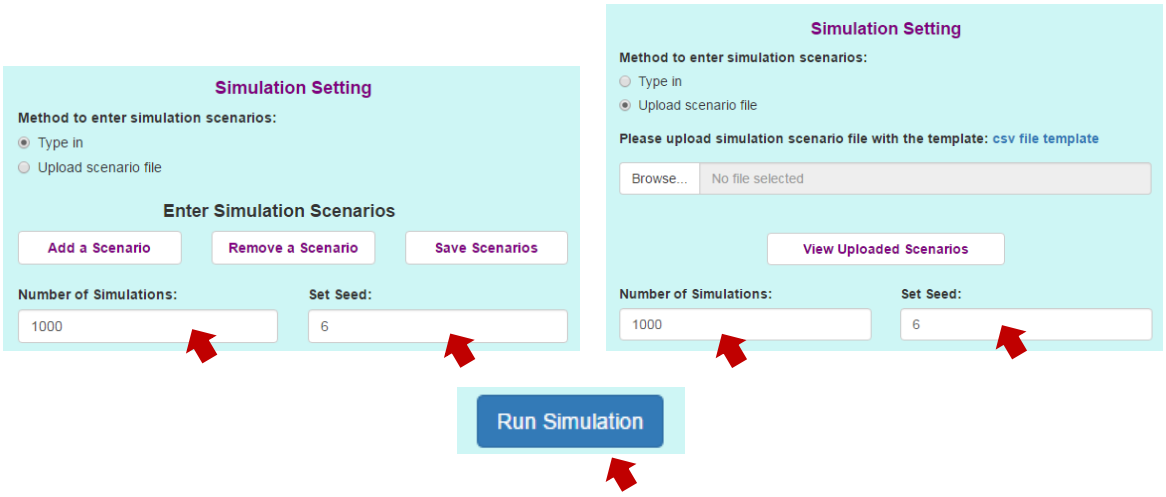
	B1	B2	B3	B4	B5
A1	0.04	0.08	0.11	0.15	0.30
A2	0.06	0.09	0.12	0.30	0.47
A3	0.09	0.11	0.30	0.45	0.59

	B1	B2	B3	B4	B5
A1	0.02	0.06	0.09	0.13	0.30
A2	0.07	0.10	0.12	0.30	0.45
A3	0.12	0.30	0.45	0.51	0.57

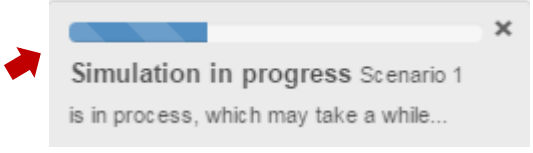
If “**Upload scenario file**” is selected, upload scenarios using the template downloadable through “**csv file template**”. Scenarios uploaded can be viewed by clicking the “**View uploaded Scenarios**” button.



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

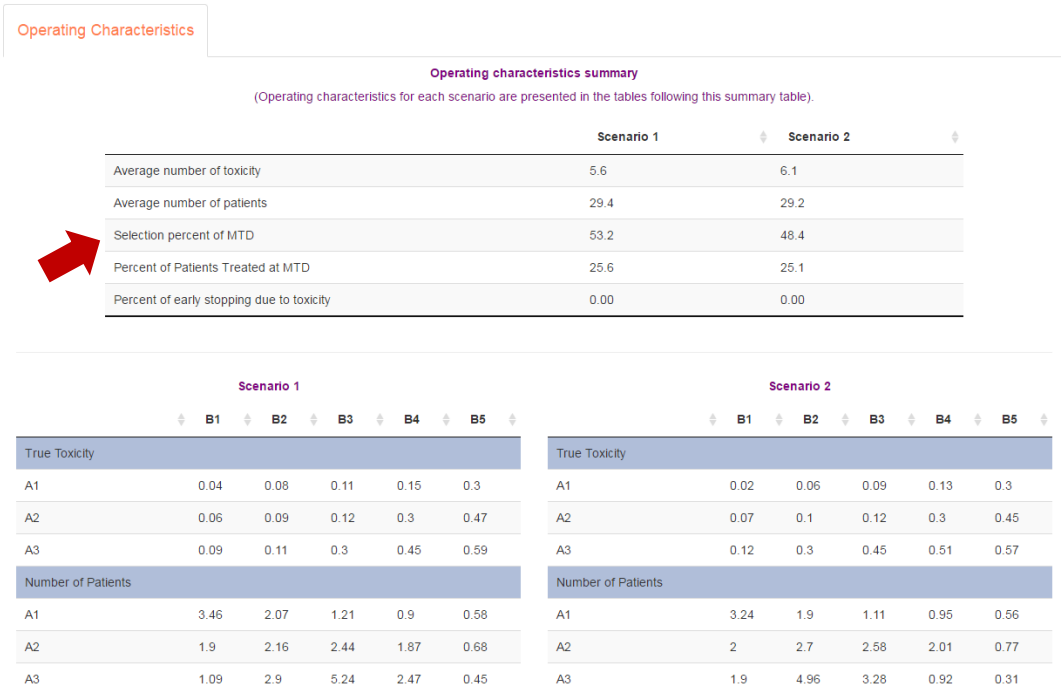


While the simulation is in process, an indicator on the bottom right of the screen shows the progress of the simulation.



The simulation results will appear in the output panel under the "Operating Characteristics" tab. The categories in the first summary table are different depending on the trial purpose.

i. When the design purpose is to find a **Single MTD**:



Operating Characteristics

Operating characteristics summary

(Operating characteristics for each scenario are presented in the tables following this summary table).

	Scenario 1	Scenario 2
Average number of toxicity	5.6	6.1
Average number of patients	29.4	29.2
Selection percent of MTD	53.2	48.4
Percent of Patients Treated at MTD	25.6	25.1
Percent of early stopping due to toxicity	0.00	0.00

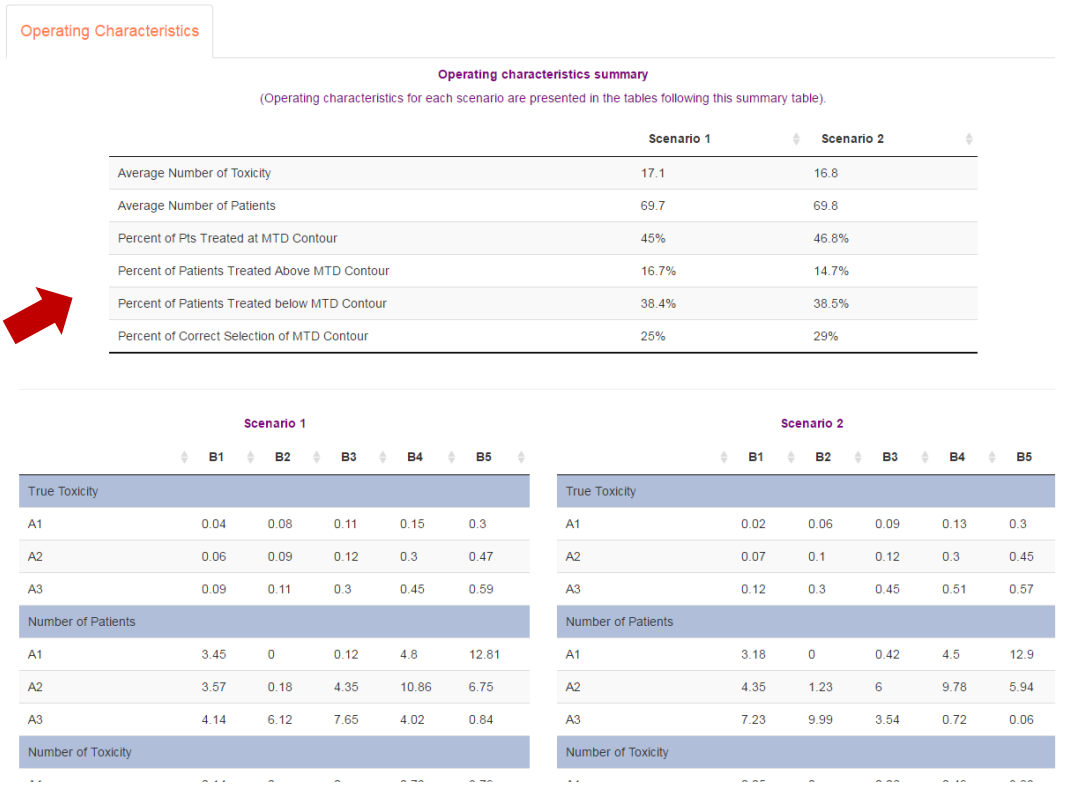
Scenario 1

	B1	B2	B3	B4	B5
True Toxicity					
A1	0.04	0.08	0.11	0.15	0.3
A2	0.06	0.09	0.12	0.3	0.47
A3	0.09	0.11	0.3	0.45	0.59
Number of Patients					
A1	3.46	2.07	1.21	0.9	0.58
A2	1.9	2.16	2.44	1.87	0.68
A3	1.09	2.9	5.24	2.47	0.45

Scenario 2

	B1	B2	B3	B4	B5
True Toxicity					
A1	0.02	0.06	0.09	0.13	0.3
A2	0.07	0.1	0.12	0.3	0.45
A3	0.12	0.3	0.45	0.51	0.57
Number of Patients					
A1	3.24	1.9	1.11	0.95	0.56
A2	2	2.7	2.58	2.01	0.77
A3	1.9	4.96	3.28	0.92	0.31

ii. When the design purpose is to find a **MTD Contour**:



Operating Characteristics

Operating characteristics summary

(Operating characteristics for each scenario are presented in the tables following this summary table).

	Scenario 1	Scenario 2
Average Number of Toxicity	17.1	16.8
Average Number of Patients	69.7	69.8
Percent of Pts Treated at MTD Contour	45%	46.8%
Percent of Patients Treated Above MTD Contour	16.7%	14.7%
Percent of Patients Treated below MTD Contour	38.4%	38.5%
Percent of Correct Selection of MTD Contour	25%	29%

Scenario 1

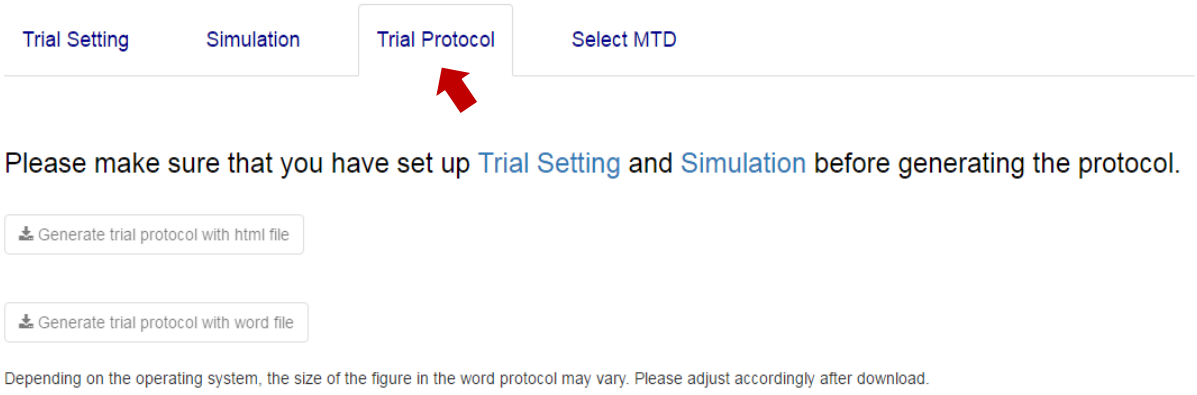
	B1	B2	B3	B4	B5
True Toxicity					
A1	0.04	0.08	0.11	0.15	0.3
A2	0.06	0.09	0.12	0.3	0.47
A3	0.09	0.11	0.3	0.45	0.59
Number of Patients					
A1	3.45	0	0.12	4.8	12.81
A2	3.57	0.18	4.35	10.86	6.75
A3	4.14	6.12	7.65	4.02	0.84
Number of Toxicity					

Scenario 2

	B1	B2	B3	B4	B5
True Toxicity					
A1	0.02	0.06	0.09	0.13	0.3
A2	0.07	0.1	0.12	0.3	0.45
A3	0.12	0.3	0.45	0.51	0.57
Number of Patients					
A1	3.18	0	0.42	4.5	12.9
A2	4.35	1.23	6	9.78	5.94
A3	7.23	9.99	3.54	0.72	0.06
Number of Toxicity					

3. Generate trial design protocol

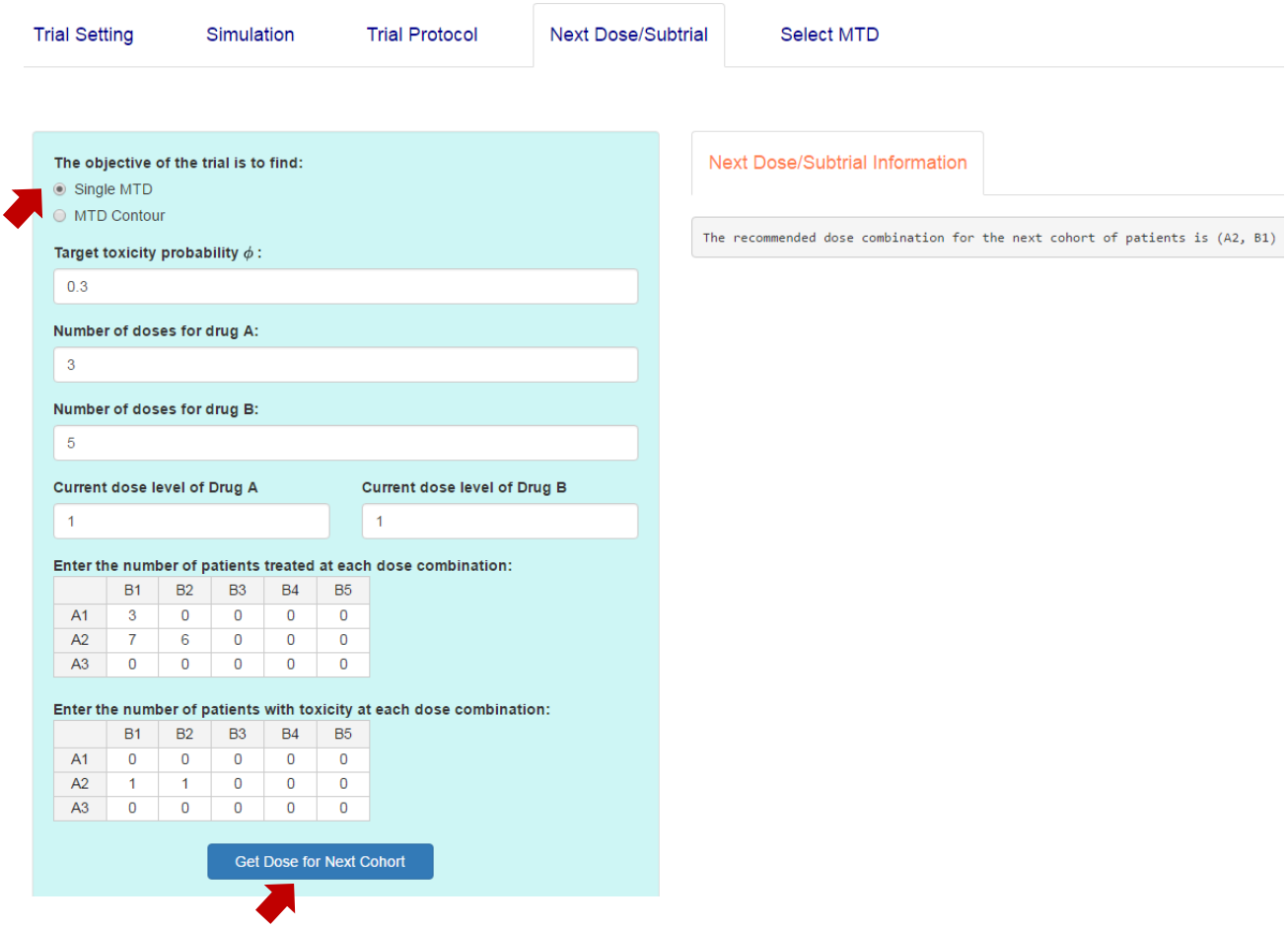
After completing the simulation (*see page 7-9*), the protocol template can be downloaded under the "Trial Protocol" Tab. The protocol template is available as an html file or word file. Depending on user's version of Word, one format may be preferable than the other.



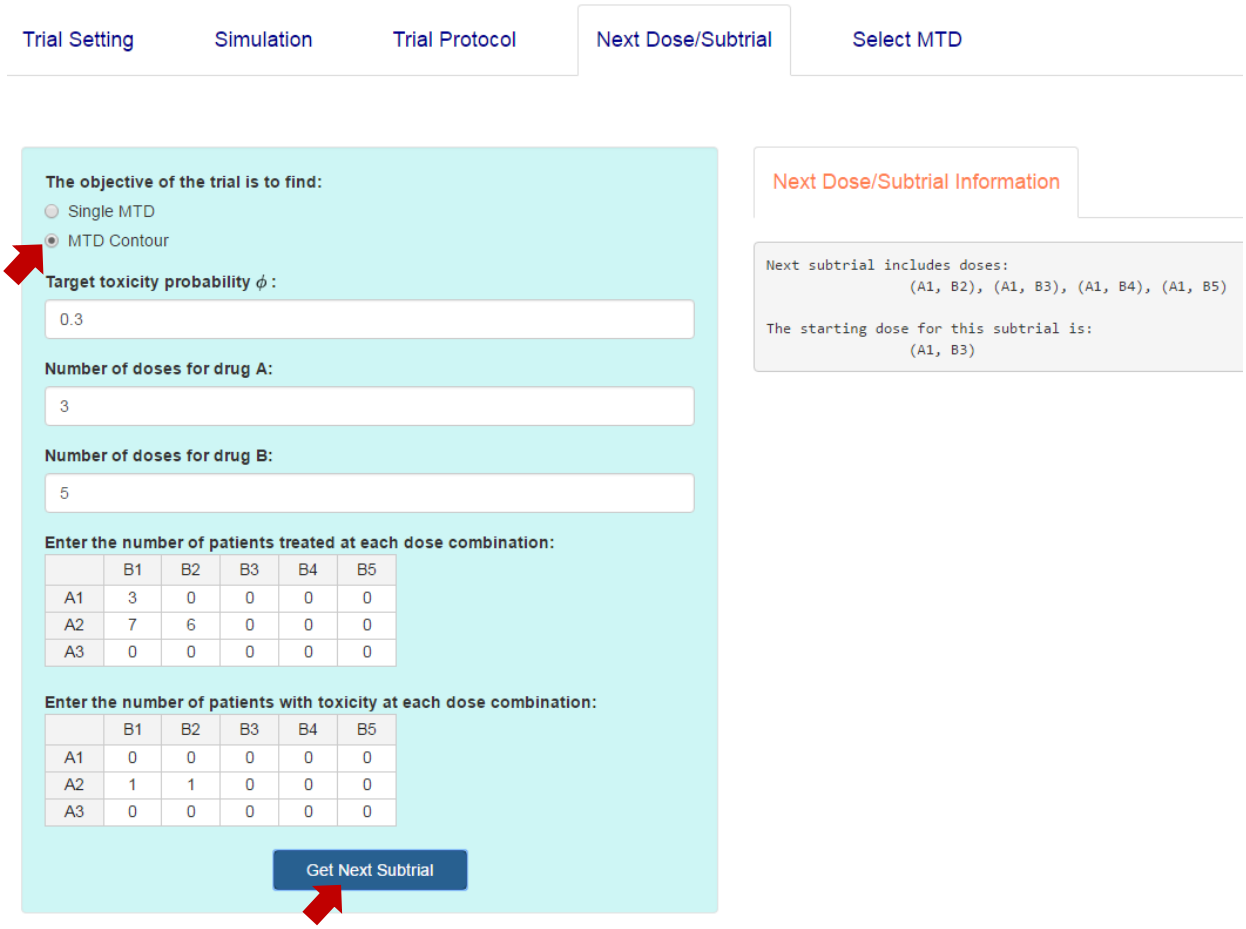
4. Conduct the trial

Conduct the trial using "Next Dose/Subtrial" tab.

a) When the trial objective is to find a single MTD, choose "**Single MTD**", enter the current observed data, and then click "**Get Dose for Next Cohort** " to obtain the dose assignment for the next new patient.



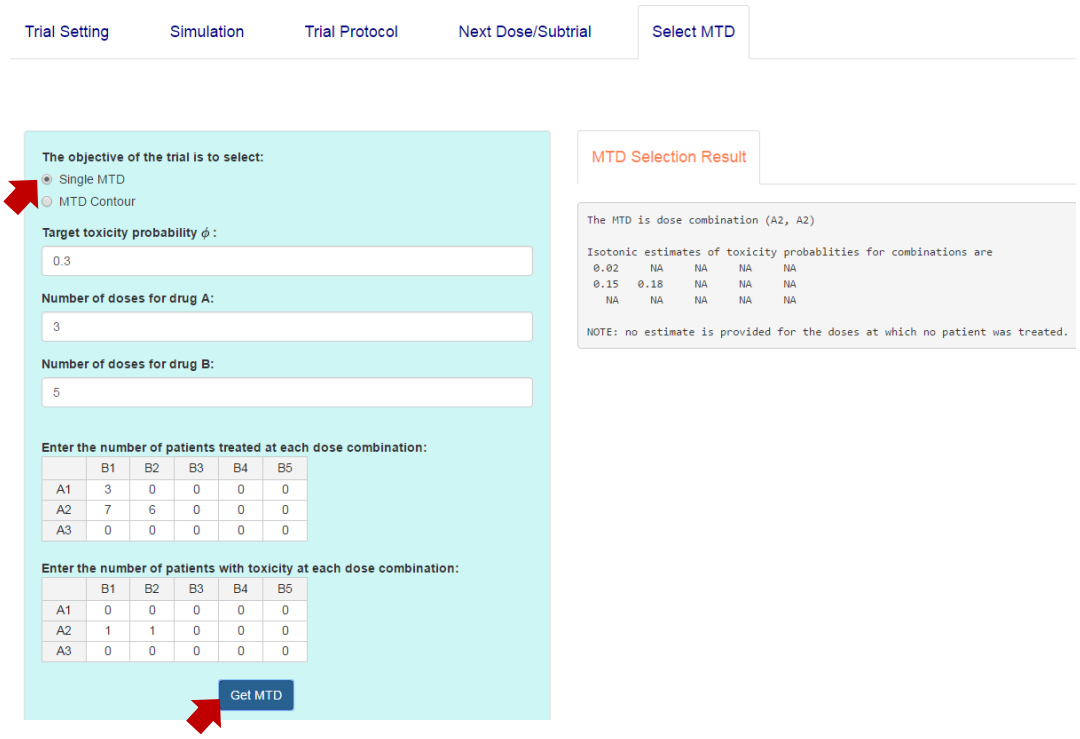
b) When the trial objective is to find the MTD contour, choose "**MTD Contour**", enter the current observed data for previous subtrial/subtrials, and click "**Get Next Subtrial**" to find the range of doses and starting dose for next subtrial. The determined subtrial is then conducted using the BOIN decision table produced in Step 1 (*see page 2-6*).



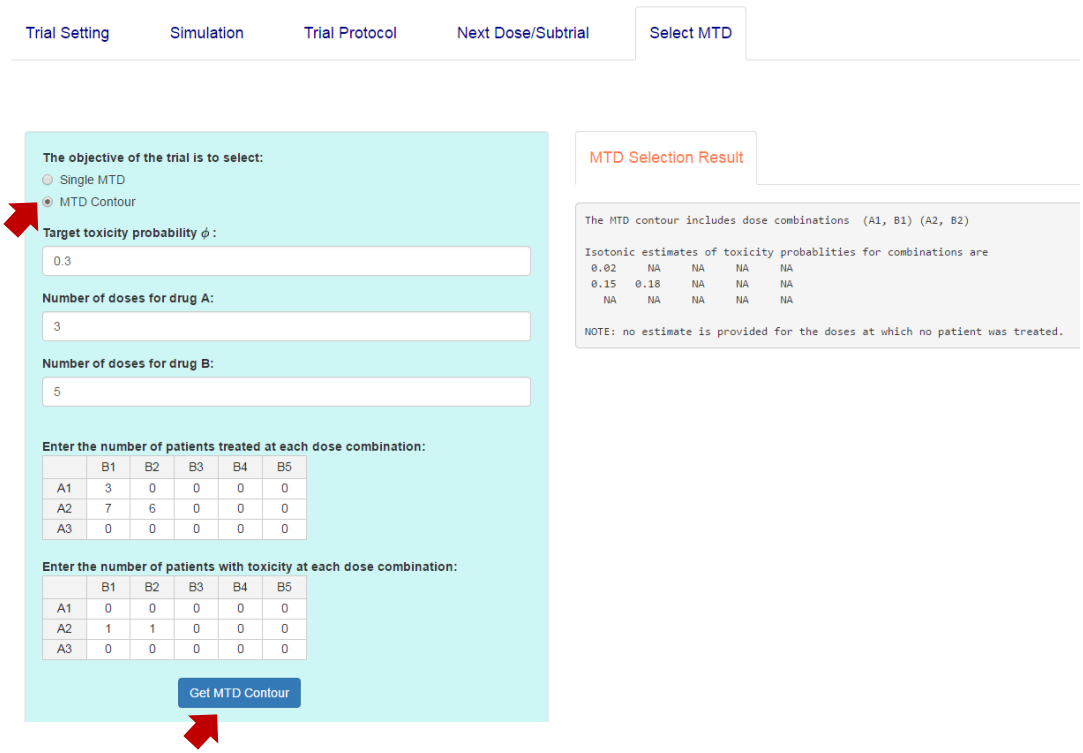
5. Select the MTD or MTD contour

After the trial is completed, click the "Select MTD" tab, choose the objective of the trial, enter observed trial data, and obtain the result by clicking

a) "**Get MTD**" if the trial purpose is to find a single MTD;



b) "**Get MTD Contour**" if the trial purpose is to find MTD Contour.



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.

Lin R. and Yin, G. (2015). Bayesian Optimal Interval Design for Dose Finding in Drug-combination Trials, *Statistical Methods in Medical Research*, DOI: 10.1177/0962280215594494.

Zhang, L. and Yuan, Y. (2016) A Practical Bayesian Design to Identify the Maximum Tolerated Dose Contour for Drug Combination Trials. *Statistics in Medicine*, **35**, 4924-4936.