



# Next Generation Dose Finding

*Quick Start Guide 1.0*



*Shengjie Yang, Sue-Jane Wang, Yuan Ji*

*December, 2014*

# Contents

- Module I: DECISION ..... 1
  - 1.1 Generate decision table ..... 1
  - 1.2 Calibration ..... 3
  - 1.3 Decide MTD ..... 5
- Module II: SIMULATION ..... 6
  - 2.1 Construct Scenarios ..... 6
  - 2.2 Modify Scenarios ..... 8
  - 2.3 Trial Simulation ..... 9
- Module III: COMPARISON ..... 11
  - 3.1 Performance Evaluation ..... 11
- References ..... 12

# Module I: DECISION

## 1.1 Generate decision table

This function generates a decision table based on the modified toxicity probability interval, or the mTPI design[1, 2], which can be used to implement a phase I dose-finding trial.

### Instructions:

Enter trial design parameters (Figure 1),

Figure 1 Input arguments



**Generate Decision Table** [Help](#)

Sample size (<=50):  Target probability:  epsilon 1:  epsilon 2:

**Sample size ( $n$ ):** The maximum number of patients to be treated at a dose level. Here, we assume an extreme case that all patients are treated at same dose level and the hard limit is set at 50 since most phase I trials do not use a large number of patients. For most cases, users can input a number much smaller than the maximum sample size, e.g., 10, which will be sufficient to monitor a phase I trial.

**Target probability ( $p_T$ ):** The target toxicity probability of the maximum tolerated dose (MTD). The goal of phase I clinical trials is to find the highest dose with a toxicity probability closest to the target probability.

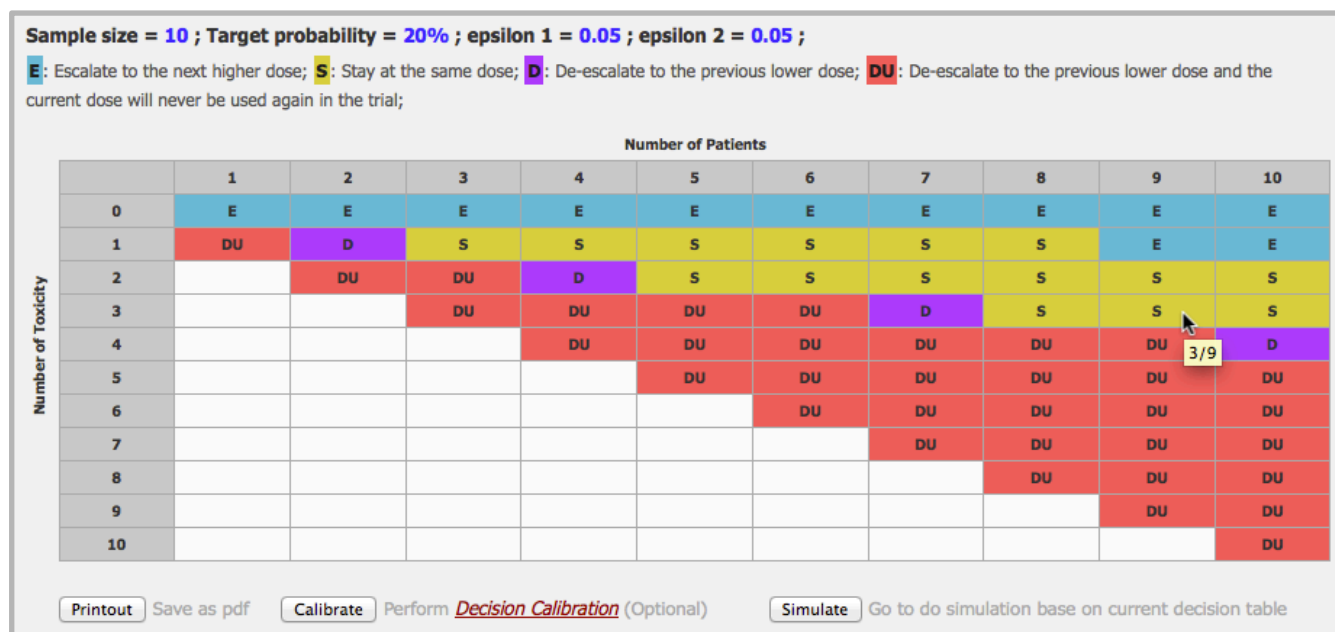
**epsilon 1 / epsilon 2 ( $\epsilon_1, \epsilon_2$ ):** Two small fractions used to define an equivalence interval of the MTD (default by 0.05 in mTPI). Any doses with a toxicity probability falling into the interval  $(p_T - \epsilon_1, p_T + \epsilon_2)$  will be considered an acceptable dose level as MTD.

After providing the two arguments, click **Submit** button. A decision table will be generated (Figure2).

The 3+3 decision table is fixed. See Fig.1 of the main paper.

The decision tables under CRM cannot be easily summarize since the dose-assignment decisions under CRM for a given outcome (say, 1 DLT out of 3 patients) and a given dose are random, depending on existing data in the entire trial including those at other doses. In other words, CRM would **stay**, **escalate** or **de-escalate** when seeing 1 out of 3 patients having the DLT at a dose, which makes it impossible to provide a fixed decision table.

**Figure 2 Decision table**



In the decision table, each column represents the number of patients treated at the current dose, the dose that is being used to treat patients in the trial, and each row represents the number of patients among the treated at the current dose who have experienced dose-limiting toxicity (DLT) events. It's the count of patients, not events.

Each cell in the table provides the dose-assignment decision based on the data readout from the row and column numbers. For example, for row 1 and column 3, i.e., 1 out of 3 patients experienced DLTs, the decision is **S**. The letters in the table represent different dose-assignment decision. **E** stands for escalating to the next higher dose, **S** stands for staying at the current dose, **D** stands for de-escalating to the next lower dose, **DU** stands for de-escalating to the next lower dose and marking the current dose as unacceptable so that it will never be used again in the remainder of the trial. Different background colors are used to distinguish different decisions.

In addition, the website will show the row and column numbers when hovering the mouse pointer over each cell. It is useful for looking over a large decision table.

## 1.2 Calibration

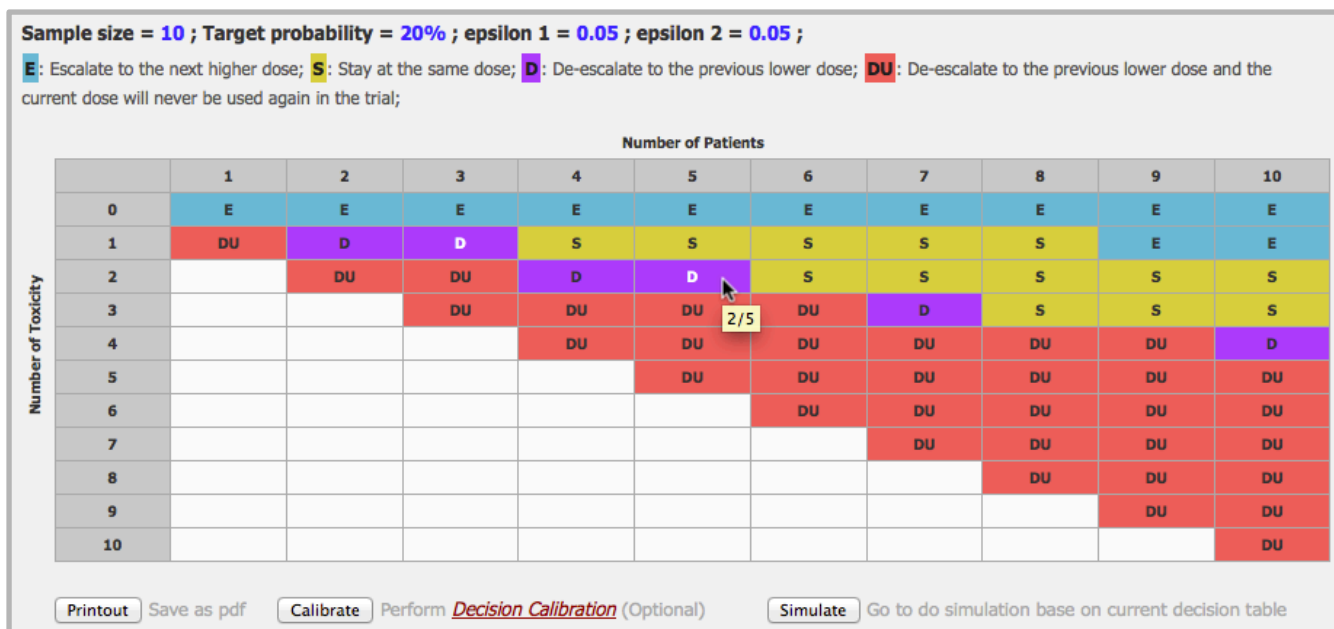
The decision table under mTPI allows users to examine all the decisions prior to the trial onset. Occasionally users may not agree with the decisions provided in the table. One may wish to change a decision from S to D, for example. This requires calibrating the mTPI design, which is now made available.

### Instructions:

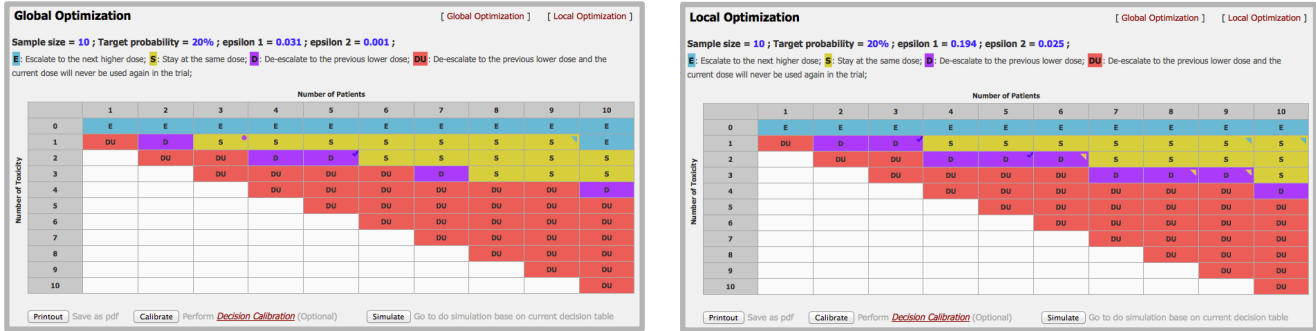
Assume a decision table has been generated (e.g, the one in Figure 2). All the cells in the table are clickable by mouse, and by clicking, one can modify the decisions. Click on cells one wishes to modify until desirable decisions are achieved. After completing all the modifications, click the **Calibrate** button to start calibrating (Figure 3). Depending on the table size, it might take up to a few minutes to complete.

As an arbitrary example, observe that 1/3 and 2/5 (row/col) are **S** in Figure 2, which means next treatment should stay at the current dose level. One might choose a more conservative decision like **D**, de-escalate. Base on this judgement, users just need to move mouse to the two corresponding cells and click these to change **S** to **D** (Figure 3). Notice that unchanged decision letters are black and changed decision letters are white. In this way, users can easily distinguish the changed vs unchanged decisions. Now click the **Calibrate** button at the bottom of the decision table to launch the calibration procedure. In return users will be provided two new tables in a few seconds. One is based on Global Optimization, which minimizes the differences between the mTPI decision table and the user-specified table on all cells; the other table is based on Local Optimization, which minimizes the differences between the mTPI decision table and user-specified table on those changed cells (Figure 4). At this point, users can choose the the global table, local table, or the original mTPI table, each of which will be compared in the simulation studies later.

**Figure 3 Calibration**



**Figure 4 Global and Local Optimization**



Symbols and colors are used to display the calibration results. Click on the “Decision Calibration” (Figure 4) will show the descriptions for these symbols:

**Symbols in Table:**

◀ : False changes. The original cell that was not asked to change but changed in the new table.

● : False non-changes. The cell that was asked to change but did not change.

≠ : Wrong changes. The cell that was asked and did change, but changed to a different decision from the desired.

✓ : True and right changes. The cell that was asked to change and changed to the desired decision.

\* The color of symbols reflects the original decision.

If users want to turn **S** to **D** but the calibration returns **DU**, we consider this a true and correct modification. In addition, users can repeat the calibration process based on the new decision table.

Here, we allow the users to freely modify each decision cell in the decision table, which would result in new rule-based designs. Such designs are no longer protected by the statistical models and principled inference under mTPI but might reflect the users’ preference. The new designs must be tested by simulation and comparison, which can be done immediately within NextGen-DF using the Simulation module next.

When the decision table is ready for simulation, click **Simulate** button. It will jump to the Simulation page and let the users simulate the trials based on the customized decision table (see also 2.3) or compare the performance with other designs (see also 3.1).

## 1.3 Decide MTD

Base on the Pool Adjacent Violators Algorithm (PAVA) [2, 3], NextGen-DF estimates the MTD when the trial is completed and data are collected.

### Instructions:

Input the number of patients treated and the number of experienced toxicity at each dose level (Figure 5).

**Figure 5 Decide MTD: Input Arguments**

Dose Level	1	2	3	4	5	6	7	8	9	10
# of Toxic	0	0	1	1	4	4				
# of Treated	3	3	3	3	9	9				
Target prob.	0.2									

Click **Submit** button. The highlighted dose with black shade is the estimated MTD (Figure 6), which is estimated based on the mTPI design using PAVA.

**Figure 6 Decide MTD: Return results**

**REPORT:** Target probability: 0.2 ; the MTD is dose **3**

Dose Level	1	2	3	4	5	6
# of Toxic	0	0	1	1	4	4
# of Treated	3	3	3	3	9	9

# Module II: SIMULATION

The decision tables generated in Sections 1.1 or 1.2 must be tested via simulations. The second module performs trial simulation to examine the operating characteristics of different designs, including mTPI, user-specified designs, 3+3 and CRM [4, 5].

## 2.1 Construct Scenarios

Simulated trials are generated under scenarios that specify true toxicity probabilities for the experimental doses. Scenarios can be constructed using two different means. **Add Single Scenario** can append scenario one by one and **Add Multiple Scenarios** can batch add multiple scenarios.

### Instructions:

In **Add Single Scenario**, users can enter **sample size** (maximum is 50), **target toxicity probability**, **epsilon 1**, **epsilon 2** (epsilon default by 0.05), **cohort size**, **number of simulated trials** (maximum is 10,000) and **dose level** (maximum is 20), then click **Add** button to add (Figure 7).

Manual input of multiple scenarios could be time consuming. Instead NextGen-DF offers a handy function that automatically generates scenarios based on the principle stated in Ji et al., 2012[6]. In the **Default Dose Level** tab (red frame in Figure 7), the numeric button stands for the number of dose levels in the simulated trials. Clicking on each number will add a default set of scenarios with that number of doses.

Figure 7 Add Single Scenario

**Add Single Scenario**

Maximum Sample Size ( $n$ ):

Cohort Size ( $co$ ):

Target Toxicity Probability ( $p_T$ ):

Dose Level:

dose 1:

dose 2:

dose 3:

epsilon 1 ( $\epsilon_1$ ):

epsilon 2 ( $\epsilon_2$ ):

Number of Simulated Trials ( $sn$ ):

Default Dose Level:



In **Add Multiple Scenarios**, users can provide multiple scenarios with **sample size** (maximum is 50), **target toxicity probability**, **epsilon 1**, **epsilon 2**, **cohort size**, **number of simulated trials** (maximum is 10,000) and **dose level** (maximum is 20). Make sure that the format of each scenario takes one line and the order of parameters follows as **sample size**, **target toxicity probability**, **epsilon 1**, **epsilon 2**, **cohort size**, **number of simulated trials**, **dose level**. Separate each parameter by a **TAB** or a **SPACE**. Then click **Add** button to add (Figure 8).

Figure 8 Add Multiple Scenarios

Add Multiple Scenarios

30	0.1	0.05	0.05	3	1000	0.02	0.04	0.08	0.12	0.17	0.25
30	0.1	0.05	0.05	3	1000	0.02	0.04	0.07	0.1	0.15	0.2
30	0.1	0.05	0.05	3	1000	0.1	0.15	0.2	0.25	0.3	0.35
30	0.1	0.05	0.05	3	1000	0.01	0.03	0.05	0.06	0.08	0.1
30	0.2	0.05	0.05	3	1000	0.02	0.05	0.08	0.11	0.14	0.17
30	0.2	0.05	0.05	3	1000	0.25	0.35	0.4	0.5	0.6	0.7
30	0.2	0.05	0.05	3	1000	0.01	0.2	0.4	0.6	0.8	0.95

\* Each scenario must be separated by **LINE BREAK**, and the parameters of each scenario must be separated by **TAB** or **SPACE**.  
The format of parameters must follow this:

```
n pT ε1 ε2 co sn dose1 dose2 .....
n pT ε1 ε2 co sn dose1 dose2 .....
.....
```

\* This will replace the existing scenarios

After providing scenarios by either **Add Single Scenario** or **Add Multiple Scenarios**, the scenarios will be displayed on the Simulation page (Figure 9). The maximum number of scenarios allowed is set to 50.

Figure 9 Display Scenarios

**Simulation Trials** Help

**Scenario 1**

<i>n</i>	<i>p<sub>T</sub></i>	<i>ε<sub>1</sub></i>	<i>ε<sub>2</sub></i>	<i>co</i>	<i>sn</i>	<i>Dose level</i>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>
30	0.1	0.05	0.05	3	1000	<i>Tox prob.</i>	0.1	0.15	0.2	0.25	0.3	0.35

**Scenario 2**

<i>n</i>	<i>p<sub>T</sub></i>	<i>ε<sub>1</sub></i>	<i>ε<sub>2</sub></i>	<i>co</i>	<i>sn</i>	<i>Dose level</i>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>
30	0.2	0.05	0.05	3	1000	<i>Tox prob.</i>	0.01	0.2	0.4	0.6	0.8	0.95

mTPI
  3+3
  CRM
  Customized

\* CRM: Make sure *n* must be multiple of *cn* and it may take around 2 mins

## 2.2 Modify Scenarios

Scenarios can be modified after being added. This allows for flexible and frequent changes in practice.

### Instructions:

Clicking **Delete** button at the bottom of scenario list (Figure 9) will remove all the existing scenarios.

Clicking **Modify** button will allow users to move, delete, and change any numbers in the scenarios (Figure 10). Afterwards, click **Submit** button to complete the modification.

Figure 10 Modify Scenarios

**Modify Scenario** [Help](#)

#	$n$	$p_T$	$\epsilon_1$	$\epsilon_2$	$co$	$sn$	dose	1	2	3	4	5	6			
1	30	0.1	0.05	0.05	3	1000	Prob.	0.05	0.07	0.09	0.11	0.13	0.15	up	down	delete
2	30	0.1	0.05	0.05	3	1000	Prob.	0.01	0.03	0.05	0.07	0.09	0.11	up	down	delete
3	30	0.1	0.05	0.05	3	1000	Prob.	0.02	0.04	0.08	0.12	0.17	0.25	up	down	delete
4	30	0.1	0.05	0.05	3	1000	Prob.	0.02	0.04	0.07	0.1	0.15	0.2	up	down	delete
5	30	0.1	0.05	0.05	3	1000	Prob.	0.1	0.15	0.2	0.25	0.3	0.35	up	down	delete
6	30	0.1	0.05	0.05	3	1000	Prob.	0.01	0.03	0.05	0.06	0.08	0.1	up	down	delete
7	30	0.2	0.05	0.05	3	1000	Prob.	0.02	0.05	0.08	0.11	0.14	0.17	up	down	delete
8	30	0.2	0.05	0.05	3	1000	Prob.	0.25	0.35	0.4	0.5	0.6	0.7	up	down	delete
9	30	0.2	0.05	0.05	3	1000	Prob.	0.01	0.2	0.4	0.6	0.8	0.95	up	down	delete
10	30	0.2	0.05	0.05	3	1000	Prob.	0.04	0.06	0.08	0.1	0.2	0.5	up	down	delete
11	30	0.2	0.05	0.05	3	1000	Prob.	0.05	0.5	0.8	0.9	0.95	0.99	up	down	delete
12	30	0.2	0.05	0.05	3	1000	Prob.	0.01	0.05	0.1	0.5	0.7	0.9	up	down	delete
13	30	0.3	0.05	0.05	3	1000	Prob.	0.35	0.45	0.5	0.6	0.7	0.8	up	down	delete
14	30	0.3	0.05	0.05	3	1000	Prob.	0.01	0.3	0.55	0.65	0.8	0.95	up	down	delete
15	30	0.3	0.05	0.05	3	1000	Prob.	0.04	0.06	0.08	0.1	0.3	0.6	up	down	delete
16	30	0.3	0.05	0.05	3	1000	Prob.	0.05	0.6	0.8	0.9	0.95	0.99	up	down	delete
17	30	0.3	0.05	0.05	3	1000	Prob.	0.01	0.05	0.1	0.6	0.7	0.9	up	down	delete
18	30	0.3	0.05	0.05	3	1000	Prob.	0.01	0.03	0.07	0.1	0.15	0.75	up	down	delete

## 2.3 Trial Simulation

This function conducts trial simulations with comparison to up to four methods (mTPI, 3+3, CRM and Customized). Customized design represents the calibrated design from Section 1.3.

### Instructions:

Check one box   mTPI  3+3  CRM  Customized (Figure 9, mTPI by default) and click **Simulate** button to perform simulation using the corresponding design.

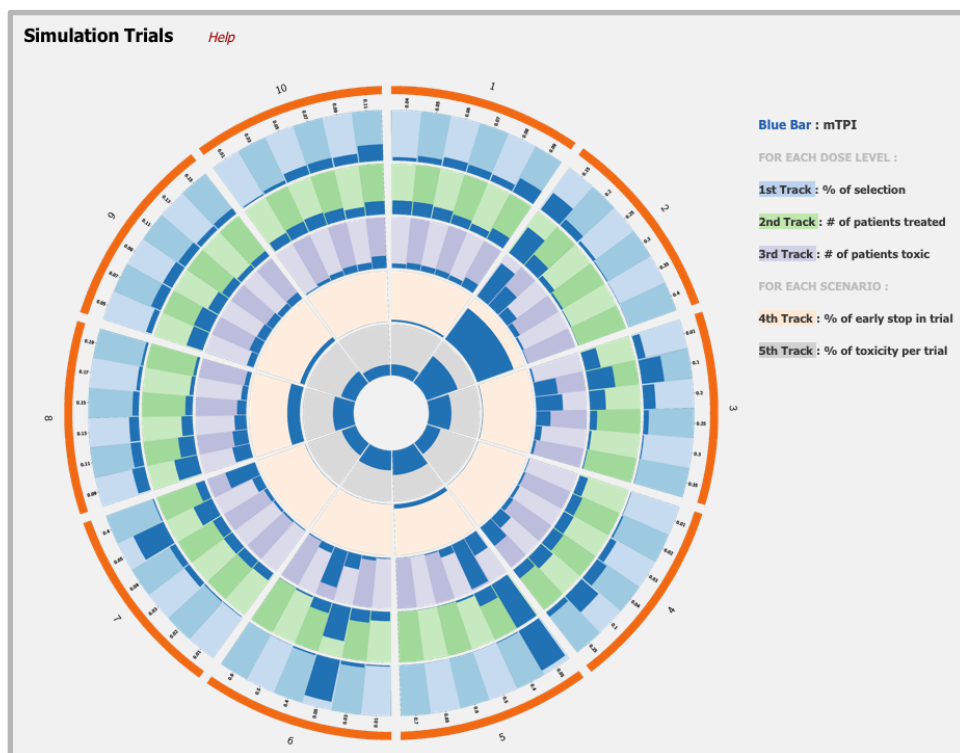
\* CRM is implemented by a R package call 'dfcrm' [4], which was developed by Ken Cheung and Jimmy Duong. It requires that sample size must be a multiple of cohort size. In addition, because CRM would take much longer time than other design, NextGen-DF will estimate the approximate elapsed time of the simulation study based on the CRM design for your information.

\* Customized requires that users submit the customized decision table at Decision page previously (Section 1.3). Otherwise, it would not be available. In addition, users can click the "Help" on the Simulation page to check the current customized decision table.

The results of simulation consist of two parts, a circo plot [7] and summary tables.

In the circo plot, five circles are used to represent the five summary statistics obtained from the simulation. Figure 11 presents an example based on the simulation using one design

**Figure 11 Simulation results under one method: A circo plot**



Summaries are organized by scenarios. Each numbered “pie” represents a scenario. From outside inwards, the first circle provides histograms of the percentage of selecting each dose as the estimated MTD for each scenario. The second circle shows the histogram of the average number of treated patients at each dose. The third circle contains the histogram of the number of patients experienced DLTs at each dose. The fourth circle shows the percentage of stopping a trial early under each scenario. This is useful if all of the doses in the scenario are above the MTD. The fifth circle plots the overall toxicity rate defined as the fraction of simulated patients experienced DLTs among all the simulated patients.

Under the circos plot is a list of tables (Figure 12) that show the numerical values of the five statistics in the circos plot. Scrolling down each table one by one and comparing to the circos plot, one can easily examine the results in detail. The circos plot is perhaps more useful in comparing multiple designs, shown next.

**Figure 12 Simulation results: Table summary.**

<b>Scenario 1</b> Sample size: 30 Target probability: 0.1 epsilon 1: 0.05 epsilon 2: 0.05 Cohort size: 3 number of simulation: 1000 <i>mTPI</i>					
Dose Level	True Prob (tox)	Selection Prob (%)	# of Subjects Treated	# of Toxicities	
1	0.04	6.8000	6.0270	0.2180	
2	0.05	11.9000	5.9400	0.2980	
3	0.06	18.1000	5.1990	0.2800	
4	0.07	15.8000	4.0560	0.2820	
5	0.08	14.1000	3.1140	0.2360	
6	0.09	31.9000	5.3370	0.4920	
<b>Prob of Early Termination</b>			0.0140		
<b>Prob of Toxicities per Trial</b>			0.0609		

<b>Scenario 2</b> Sample size: 30 Target probability: 0.1 epsilon 1: 0.05 epsilon 2: 0.05 Cohort size: 3 number of simulation: 1000 <i>mTPI</i>					
Dose Level	True Prob (tox)	Selection Prob (%)	# of Subjects Treated	# of Toxicities	
1	0.15	43.0000	14.0280	2.0830	
2	0.2	16.9000	6.3720	1.3050	
3	0.25	6.3000	2.3220	0.6110	
4	0.3	1.7000	0.8880	0.2670	
5	0.35	0.5000	0.2940	0.1010	
6	0.4	0.0000	0.0630	0.0280	
<b>Prob of Early Termination</b>			0.3160		
<b>Prob of Toxicities per Trial</b>			0.1834		

<b>Scenario 3</b> Sample size: 30 Target probability: 0.1 epsilon 1: 0.05 epsilon 2: 0.05 Cohort size: 3 number of simulation: 1000 <i>mTPI</i>					
Dose Level	True Prob (tox)	Selection Prob (%)	# of Subjects Treated	# of Toxicities	
1	0.01	15.9000	6.8280	0.0800	
2	0.1	46.3000	11.7630	1.1560	

Show the whole result on a single page    
  Go back to scenario page

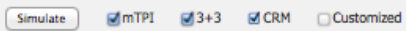
At the bottom of the table, click **Table** button to open a new page to display the entire results table. Click the **Back** button to go back to scenario page.

# Module III: COMPARISON

## 3.1 Performance Evaluation

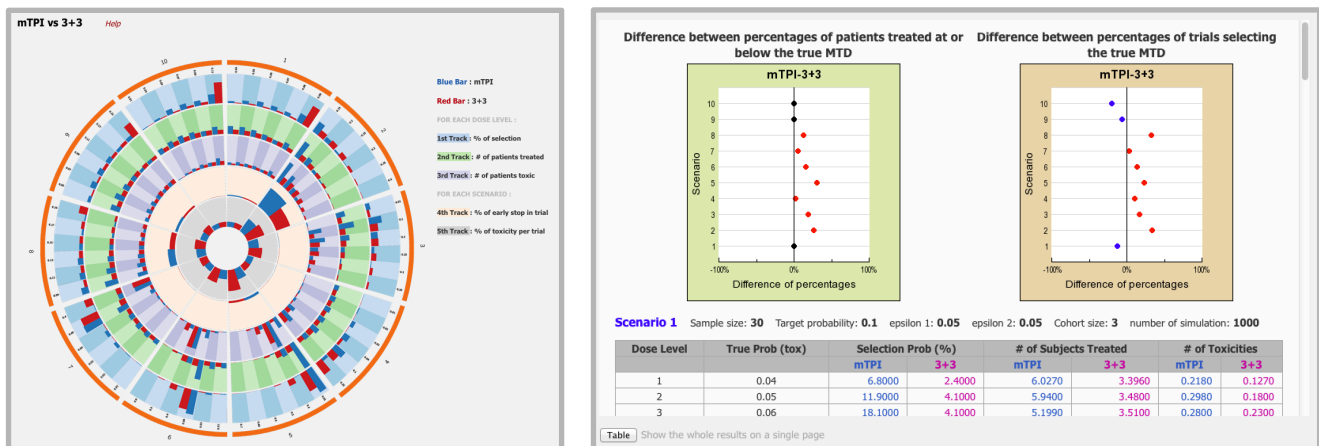
When comparing multiple methods, we first provide two summary statistics[2] to evaluate the performance of different designs.

### Instructions:

On the simulation page, check any two or three boxes  (Figure 9, mTPI by default) and click **Simulate** button to perform comparison.

The comparison report is show in Figure 13.

**Figure 13 Comparison results**



Here, the displays include a circos plot and tables of the simulation results. They just combine the comparative designs together and use different color to distinguish each other.

Two additional summaries are presented as dot plots (right hand side of Figure 13), which summarize the safety and reliability of the designs under comparison.

**Safety** : The green background chart shows the difference between the two designs on their percentages of patients treated at or below the true MTD, which evaluates the safety of the design. If the most dots are red in the chart, it suggests that the first design is safer than the second one.

**Reliability** : The brown background chart shows the difference between the two designs on their percentages of selecting the true MTD, which measures the reliability of the design. If the most dots are red in the chart, it suggests that the first design is more reliable than the second one.

# References

1. Ji Y, Liu P, Li Y, *et al.* A modified toxicity probability interval method for dose-finding trials. *Clinical Trials* 2010;7(6):653-663.
2. Ji Y, Wang S. Modified Toxicity Probability Interval Design: A Safer and More Reliable Method Than the 3+ 3 Design for Practical Phase I Trials. *Journal of Clinical Oncology* 2013;31(14):1785-2792.
3. Robertson T, Wright F, Dykstra R, *et al.* *Order restricted statistical inference*. New York: Wiley; 1988.
4. Cheung K, Duong MJ. *dfcrm: Dose-finding by the continual reassessment method*. 2013.
5. Storer BE. Design and Analysis of Phase I Clinical Trials. *Biometrics* 1989;45(3):925-937.
6. Ji Y, Feng L, Liu P, *et al.* Bayesian continual reassessment method for dose-finding trials infusing T cells with limited sample size. *Journal of biopharmaceutical statistics* 2012;22(6):1206-1219.
7. Krzywinski MI, Schein JE, Birol I, *et al.* Circos: An information aesthetic for comparative genomics. *Genome Research* 2009; 10.1101/gr.092759.109.