

Steps to use BOIN App to design a phase I trial

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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 .

Trial Setting Simulation Trial Protocol Select MTD



How to Use the BOIN App?

Doses 

Number of doses: 

Starting dose level: 

Target Probability 

Target Toxicity Probability ϕ :



Use the default alternatives to minimize decision error (recommended).

Sample Size 

Cohort size: 

Number of cohort: 

Stop trial if number of patients assigned to single dose reaches:



Overdose Control 

Eliminate dose j if $Pr(p_j > \phi \mid data) > p_E$

Use the default cutoff (recommended) $p_E =$



Check the box to impose a more stringent safety stopping rule:

[Get Flow Chart and Decision Table](#)

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.

Overdose Control ?

Eliminate dose j if $\Pr(p_j > \phi \mid data) > p_E$

Use the default cutoff (recommended) $p_E =$

 Check the box to impose a more stringent safety stopping rule:
Stop the trial if $\Pr(p_1 > \phi \mid data) > p_E - \delta$, where δ is
[Get Flow Chart and Decision Table](#)

- 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.

Overdose Control ?

Eliminate dose j if $Pr(p_j > \phi | data) > p_E$

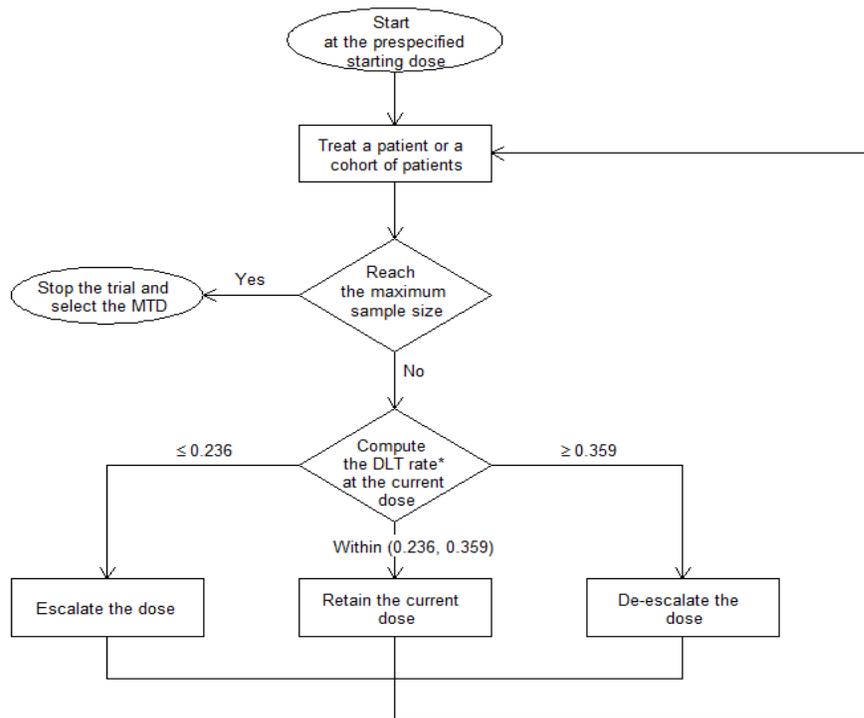
Use the default cutoff (recommended) p_E =

0.95

Check the box to impose a more stringent safety stopping rule:

Get Flow Chart and Decision Table

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.



* DLT rate = $\frac{\text{Total number of patients who experienced DLT at the current dose}}{\text{Total number of patients treated at the current dose}}$

[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

2. Obtain operating characteristics of the design.

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

Trial Setting Simulation Trial Protocol Select MTD

Simulation

Method to enter simulation scenarios:

Type in

Upload scenario file

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**”.

Simulation

Method to enter simulation scenarios:

Type in

Upload scenario file

Enter Simulation Scenarios

Add a Scenario **Remove a Scenario** **Save Scenarios**

Number of Simulations: 1000 Set Seed: 6

For each scenario, enter true toxicity rate of each dose level:

	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

Run Simulation

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.

Simulation

Method to enter simulation scenarios:

- Type in
- Upload scenario file

Please upload simulation scenario file with the template: [csv file template](#)

Browse... No file selected

View Uploaded Scenarios

Number of Simulations: 1000

Set Seed: 6

Run Simulation

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

Simulation

Method to enter simulation scenarios:

Type in
 Upload scenario file

Enter Simulation Scenarios

Number of Simulations:
Set Seed:

For each scenario, enter true toxicity rate of each dose level:

	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

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

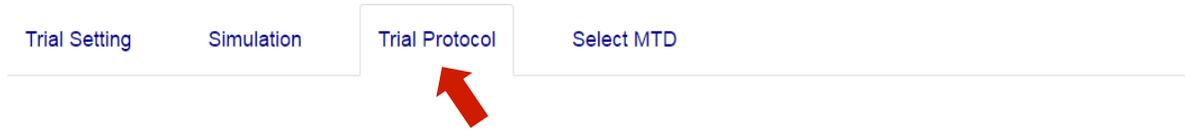
Operating Characteristics

Search:

	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.



Please make sure that you have set up [Trial Setting](#) and [Simulation](#) before generating the protocol.

 [Generate trial protocol with html file](#)

 [Generate trial protocol with word file](#)

Depending on the operating system, the size of the figure in the word protocol may vary. Please adjust accordingly after download.

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.

Trial Setting Simulation Trial Protocol **Select MTD**

Target Toxicity Probability ϕ :

0.3

Number of doses

5

Please enter the trial data:

Dose level	Number of patients treated	Number of patients with dose limiting toxicity
1	3	0
2	6	1
3	12	4
4	4	2
5	0	0

Estimate the MTD

The recommend MTD will appear on the output panel:

MTD Selection Result

The MTD is dose level 3

Dose Level	Posterior DLT Estimate	95% Credible Interval	Pr(toxicity>0.3 data)
1	0.02	(0.00 , 0.20)	0.01
2	0.17	(0.01 , 0.53)	0.18
3	0.33	(0.11 , 0.61)	0.57
4	0.50	(0.10 , 0.90)	0.79
5	----	(-----)	----

NOTE: no estimate is provided for the doses at which no patient was treated.

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.