Time-to-event Bayesian Optimal Interval Design to Accelerate Phase I Trials

Ying Yuan
Professor, Chief of Section of Adaptive Clinical Trials
MD Anderson Cancer Center

Joint work with Ruitao Lin (MDA), Daniel Li (Juno), Lei Nie (FDA) and Kathy Warren (NCI)

Outline

- Logistic difficulty associated with late-onset toxicity and fast accrual
- Time-to-event Bayesian Optimal Interval (TITE-BOIN) design
- Numerical Study
- Software

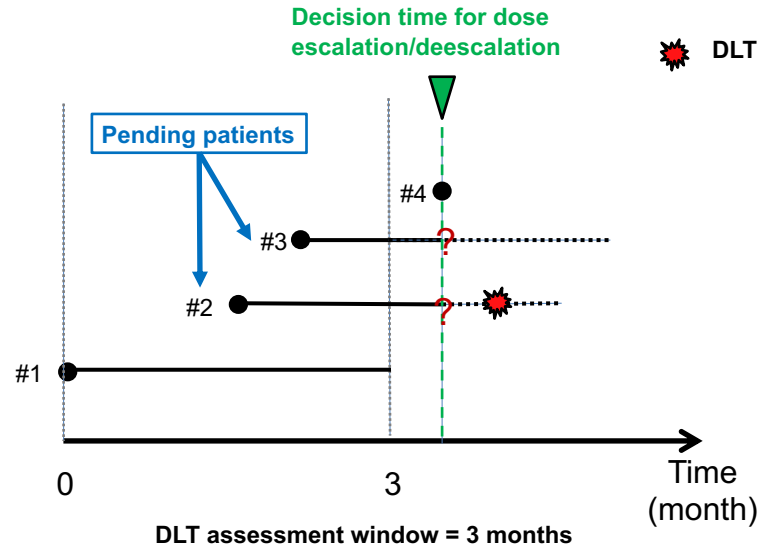
Late-onset toxicity

- Late-onset toxicity is common in the era of immunotherapy and targeted therapy.
  - In 36 clinical trials involving molecularly targeted agents, more than half of the 445 patients developed their high grade toxicity after the first cycle (Postel-Vinay et al., 2011, JCO).
  - Immuno-toxicity is often late-onset (June et al., 2017, Nat Med; Weber et al., 2015, JCO).
- Late-onset toxicity is also common in conventional radiochemotherapy.

Logistic difficulty with late-onset toxicity

- Late-onset toxicity causes a major logistic difficulty for conducting phase I trials.
- For example, if the DLT takes up to 8 weeks to evaluate and the accrual rate is 1 patient/week, on average, 5 new patients will be accrued while waiting to evaluate the previous 3 patients' outcomes.
- **Question**: How can new patients receive timely treatment when the previous patients' outcomes are pending?

Pending patients



Logistic difficulty with fast accrual

- The same logistic difficulty arises when the accrual is fast.
- Suppose that the DLT of a new agent can be assessed in the first 28-day cycle.
- If the accrual rate is 8 patients/28 days, then on average, 5 new patients will accrue while waiting to evaluate the previous 3 patients' outcomes.
- **Question**: How can new patients receive timely treatment when the previous patients' outcomes are pending?

Methods for late-onset toxicity

- **Model-based approach**: Time-to-event CRM (TITE-CRM; Cheung and Chappell, 2000), data argumentation CRM (DA-CRM; Liu et al., 2013)
  - Perform well, but are complicated to implement and subject to the influence of model misspecification
- **Algorithm-based approach**: Rolling 6 design (Skolnik et al., 2008), Rapid enrollment design (Ivanova, et al., 2016)

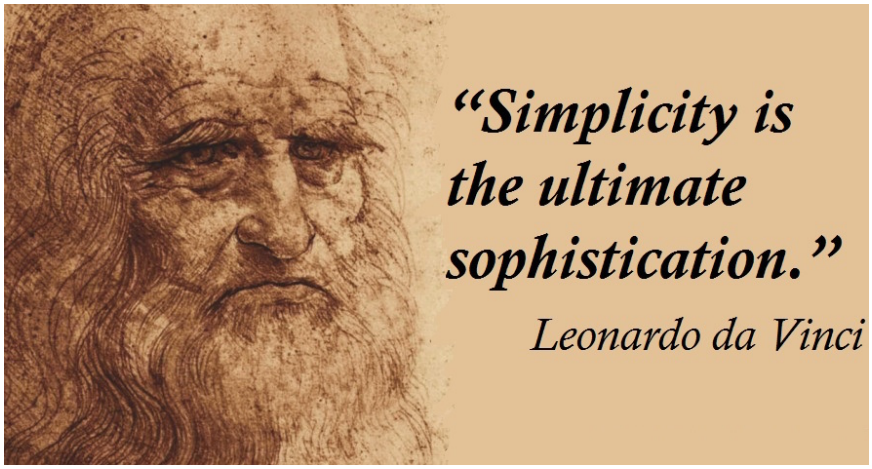
	DLT Data			Enrolling Dose Level*			
				MTD Not Exceeded		MTD Exceeded	
No. Enrolled	No. DLTs	No. Without DLT	No. With Data Pending	3 + 3	Rolling Six	3 + 3	Rolling Six
2	0, 1	Any	Any	n	n		
2	2	0	0	n − 1	n − 1		
3	0	0, 1, 2	3, 2, 1	Suspend	n		
3	0	3	0	n + 1	n + 1		
3	1	0, 1	2, 1	Suspend	n		
3	1	2	0	n	n		
3	≥ 2	Any	Any	n − 1	n − 1		

Objective

- Can we have a design that combines the good performance of the TITE-CRM with the simplicity of rolling 6 design?

→ Time-to-event BOIN (TITE-BOIN)

A model-assisted design !



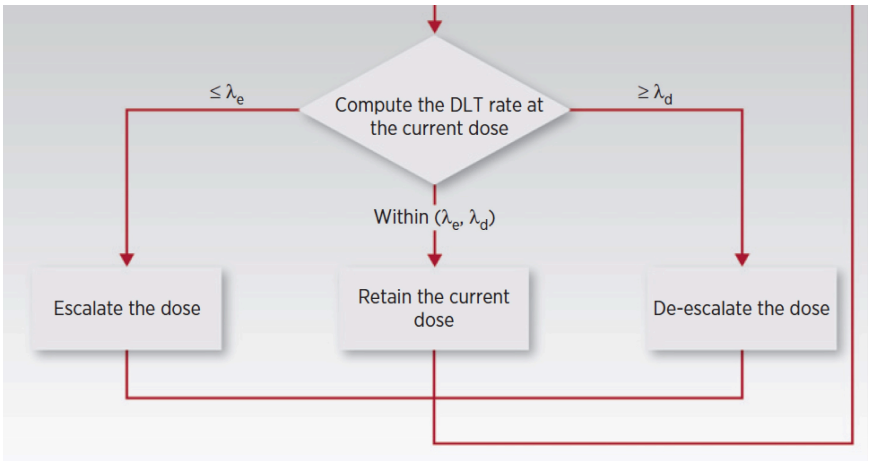
Notation

- Let T denote the pre-specified DLT assessment window
  - T should be long enough to cover all DLTs that are relevant to defining the MTD
- y_i is the DLT indicator, such that y_i = 1 if patient experiences DLT in (0, T], otherwise y_i =0
- Suppose that at a moment of decision making, n patients are enrolled at the current dose, r patients have completed the DLT assessment (i.e., their DLT data y_i are observed), denoted as O.

Notation

- $c = n - r$ patients have not completed the DLT assessment (i.e., their DLT data y_i are pending/missing).
- Denote these pending patients as M.
- $t_i (< T)$ denotes the follow-up time for the patient whose DLT data are pending, i.e., $i \in M$.

Bayesian Optimal Interval (BOIN) Design



DLT rate at the current dose $= \dfrac{\text{No. of patients experienced DLT at the current dose (ntox)}}{\text{No. of patients treated at the current dose (n)}}$

Escalation/de-escalation boundaries

Table 1. Dose escalation and de-escalation boundaries

	Target toxicity rate for the MTD						
Boundary	0.1	0.15	0.2	0.25	0.3	0.35	0.4
λ_e (escalation)	0.078	0.118	0.157	0.197	0.236	0.276	0.316
λ_d (de-escalation)	0.119	0.179	0.238	0.298	0.358	0.419	0.479

- Escalation and de-escalation boundaries λ_e and λ_d are derived to minimize the probability of making incorrect decisions of dose escalation and de-escalation.

Yuan Y, Hess K, Hilsenbeck, S and Gilbert M (2016), *Clinical Cancer Research*, 22, 4291-4301.

Escalation/de-escalation boundaries

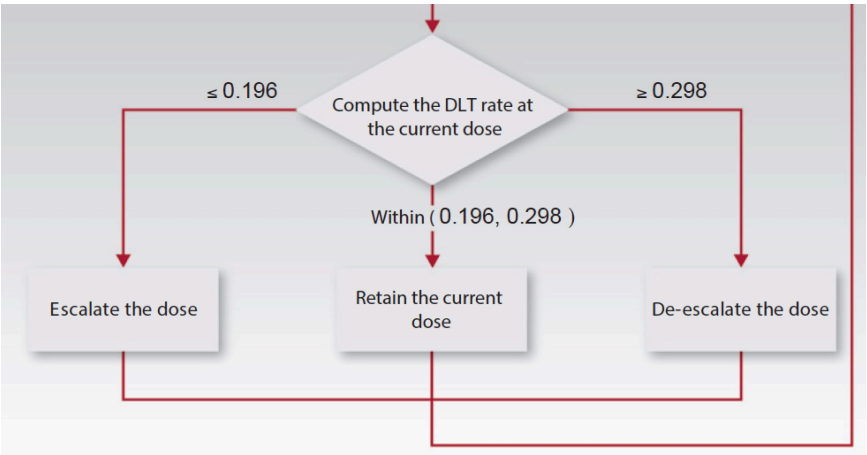
Table 1. Dose escalation and de-escalation boundaries

	Target toxicity rate for the MTD						
Boundary	0.1	0.15	0.2	**0.25**	0.3	0.35	0.4
λ_e (escalation)	0.078	0.118	0.157	**0.197**	0.236	0.276	0.316
λ_d (de-escalation)	0.119	0.179	0.238	**0.298**	0.358	0.419	0.479

- Escalation and de-escalation boundaries λ_e and λ_d are derived to minimize the probability of making incorrect decisions of dose escalation and de-escalation.

Yuan Y, Hess K, Hilsenbeck, S and Gilbert M (2016), *Clinical Cancer Research*, 22, 4291-4301.

BOIN design for target = 25%



$$\text{DLT rate at the current dose} = \frac{\text{No. of patients experienced DLT at the current dose (ntox)}}{\text{No. of patients treated at the current dose (n)}}$$

BOIN under late-onset toxicity

- BOIN makes decision based on the empirical (maximum likelihood) estimate of the toxicity rate at the current dose

$$\hat{p} = \frac{\sum_{i \in O} y_i + \sum_{i \in M} y_i}{n}$$

- **Problem**: y_i is not observed for pending patients (i.e., $i \in M$)
- **Strategy**: to replace unobserved y_i with its predicted value $\hat{y}_i$

$$\hat{p} = \frac{\sum_{i \in O} y_i + \sum_{i \in M} \hat{y}_i}{n}$$

Impute missing/pending data

- Assuming that the time to DLT X_i follows a uniform distribution over $[0, T]$, the expected value of y_i, $i \in M$, for a pending patient with follow-up time t_i is

$$\hat{y}_i = E(y_i | X_i > t_i) = \Pr(y_i = 1 \mid X_i > t_i)$$
$$= \frac{p\left(1 - \frac{t_i}{T}\right)}{p\left(1 - \frac{t_i}{T}\right) + (1 - p)} \approx \frac{p\left(1 - \frac{t_i}{T}\right)}{(1 - p)}$$

Impute missing/pending data

- Thus

$$\hat{p} = \frac{\sum_{i \in O} y_i + \sum_{i \in M} \hat{y}_i}{n}$$
$$= \frac{s + \frac{p}{1 - p}(c - \text{STFT})}{n}$$

where **STFT** $= \sum_{i \in M} t_i / T$ is the standardized total follow-up time (STFT) for pending patients at the current dose, and s is the number of patients who experienced DLT at the current dose

TITE-BOIN decision table (target=0.3)

Table S1. Dose escalation and de-escalation boundaries for TITE-BOIN with a target DLT rate of 0.3 and cohort size of 3.

No. treated	No. DLTs	No. data pending	STFT Escalate	STFT Stay	STFT De-escalate	No. treated	No. DLTs	No. data pending	STFT Escalate	STFT Stay	STFT De-escalate
3	0	≤1	Y			12	2	5	≥2.72	<2.72	
3	0	≥2	Suspend accrual			12	2	6	≥4.11	<4.11	
3	1	0	Y			12	2	≥7	Suspend accrual		
3	1	1	>0.88	≤0.88		12	3	≤6	Y		
3	1	≥2	Suspend accrual			12	3	≥7	Suspend accrual		
3	2	≤1	Y			12	4	0	Y		
3	3	0	Y&Elim			12	4	1	>0.43	≤0.43	
6	0	≤3	Y			12	4	2	>1.50	≤1.50	
6	0	≥4	Suspend accrual			12	4	3	>2.57	≤2.57	
6	1	≤1	Y			12	4	4	>3.65	≤3.65	
6	1	2	≥0.60	<0.60		12	4	5	>4.72	≤4.72	
6	1	3	≥1.96	<1.96		12	4	6	>5.79	≤5.79	
6	1	≥4	Suspend accrual			12	4	≥7	Suspend accrual		
6	2	0	Y			12	5, 6	≤7	Y		
6	2	1	>0.73	≤0.73		12	≥7	≤5	Y&Elim		
6	2	2	>1.80	≤1.80		15	0	≤7	Y		
6	2	3	>2.87	≤2.87		15	0	≥8	Suspend accrual		
6	2	≥4	Suspend accrual			15	1	≤7	Y		
6	3	≤3	Y			15	1	≥8	Suspend accrual		
6	≥4	≤2	Y&Elim			15	2	≤5	Y		
9	0	≤4	Y			15	2	6	≥0.35	<0.35	
9	0	≥5	Suspend accrual			15	2	7	≥2.07	<2.07	

TITE-BOIN decision table (target=0.3)

No. treated	No. DLTs	No. data pending	STFT Escalate	STFT Stay	STFT De-escalate
3	0	≤1	Y		
3	0	≥2	Suspend accrual		
6	0	≥4	Suspend accrual		
6	1	≤1	Y		
6	1	2	≥0.60	<0.60	
6	1	3	≥1.96	<1.96	
6	1	≥4	Suspend accrual		
6	2	0	Y		
6	2	1	>0.73	≤0.73	
6	2	2	>1.80	≤1.80	
6	2	3	>2.87	≤2.87	

STFT (Standardized Total Follow-up Time) =

$$\frac{Sum\ of\ the\ follow\ up\ time\ for\ pending\ patients\ at\ the\ current\ dose}{The\ length\ of\ DLT\ assessment\ window}$$

Incorporate prior information

- Partition the assessment window $[0, T]$ into three parts: the initial part $[0, T/3]$, the middle part $(T/3, 2T/3]$ and the final part $(2T/3, T]$
- Let (π_1, π_2, π_3) be the prior probability that the DLT would occur at the three parts of the assessment window
- Weighted STFT (WSTFT) weights follow-up time using (π_1, π_2, π_3)
- Remarkably, using an informative prior for the time to DLT does not alter the decision table!

Safety rules

- If >50% patient's DLT data are pending at the current dose, we suspend the accrual.
- During trial conduct, we impose the following overdose control / safety stopping rule:

  If $\Pr(p > \phi | y, n) > 0.95$ and $n \geq 3$, eliminate the current and higher doses from the trial; if the lowest dose is eliminated, terminate the trial early for safety.

where ϕ is the target DLT rate, and $\Pr(p_j \geq \phi | n_j, y_j)$ can be evaluated based on a beta-binomial model.

Selection of the MTD

- When the maximum sample size is reached, stop the trial and select the dose whose isotonic estimate of the toxicity rate is closest to the target ϕ as the MTD.

Simulation

- A phase I trial with 7 dose levels.
- The DLT assessment window is 3 months, the accrual rate is 2 patients/month.
- The time to DLT is sampled from a Weibull distribution, with 50% of DLTs occurring in the second half of the assessment window.
- The maximum sample size is 36 patients, treated in cohorts of 3.
- The target DLT rate = 0.2 or 0.3, with 8 representative scenarios for each rate, resulting in 16 scenarios

Scenarios

Scenario	Dose level						
	1	2	3	4	5	6	7
	Target DLT rate is 0.2						
1	0.05	**0.20**	0.46	0.50	0.60	0.70	0.80
2	0.02	0.05	**0.20**	0.28	0.34	0.40	0.44
3	0.01	0.05	0.10	**0.20**	0.32	0.50	0.70
4	0.01	0.04	0.07	0.10	0.50	0.70	0.90
5	0.01	0.05	0.10	0.14	**0.20**	0.26	0.34
6	0.01	0.02	0.03	0.05	**0.20**	0.40	0.50
7	0.01	0.04	0.07	0.10	0.15	**0.20**	0.25
8	0.01	0.02	0.03	0.04	0.05	**0.20**	0.45
	Target DLT rate is 0.3						
9	**0.30**	0.40	0.50	0.60	0.70	0.80	0.90
10	0.14	**0.30**	0.39	0.48	0.56	0.64	0.70
11	0.07	0.23	0.41	0.49	0.62	0.68	0.73
12	0.05	0.15	**0.30**	0.40	0.50	0.60	0.70
13	0.05	0.12	0.20	0.30	0.38	0.49	0.56
14	0.01	0.04	0.08	0.15	0.30	0.36	0.43
15	0.02	0.04	0.08	0.10	0.20	0.30	0.40
16	0.01	0.03	0.05	0.07	0.09	0.30	0.50

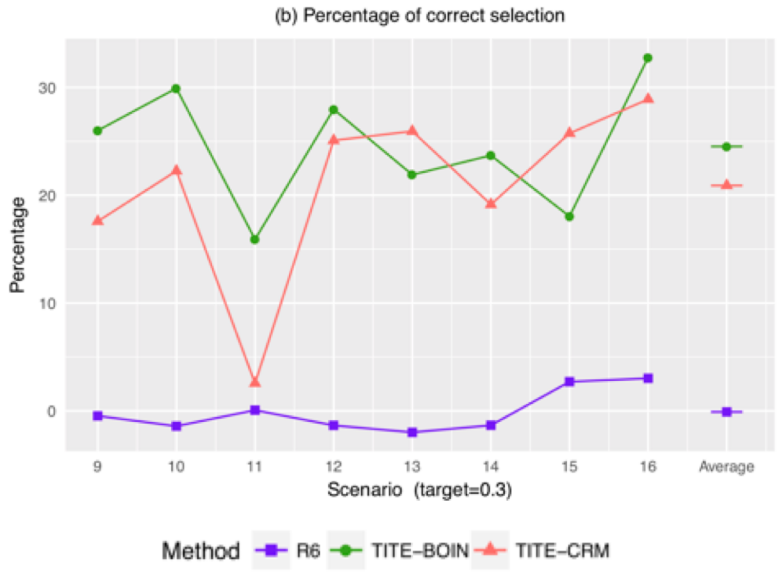
Simulation

- Compare TITE-BOIN, 3+3 design, R6 design, and TITE-CRM
- For the 3+3 design, a new cohort is enrolled only when the previous cohort's DLT data are cleared
- Because the 3+3 and R6 designs often stopped the trial early (e.g., when 2 of 3 patients experienced DLT) before reaching 36 patients, in these cases, the remaining patients are treated at the selected "MTD" as the cohort expansion, such that the four designs have comparable sample sizes

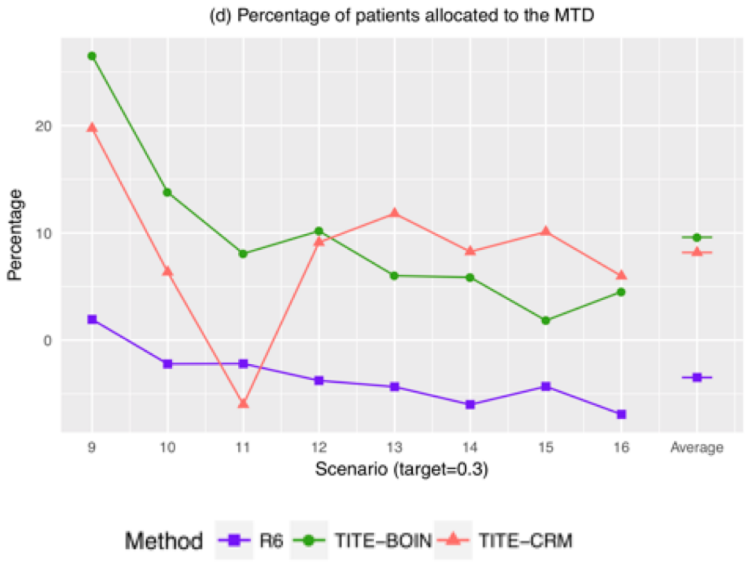
Performance metrics

- Percentage of correct selection of the MTD
- Percentage of patients allocated to the MTD
- Percentage of overdosing selection (i.e., selecting a dose above the MTD)
- Percentage of patients overdosed (i.e., treated at doses above the MTD)
- Average trial duration

Percentage of correct selection

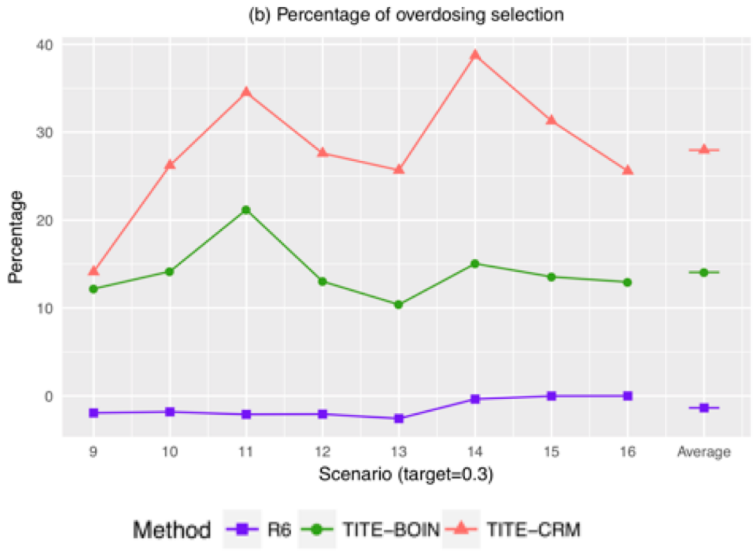


Percentage of patients treated at MTD

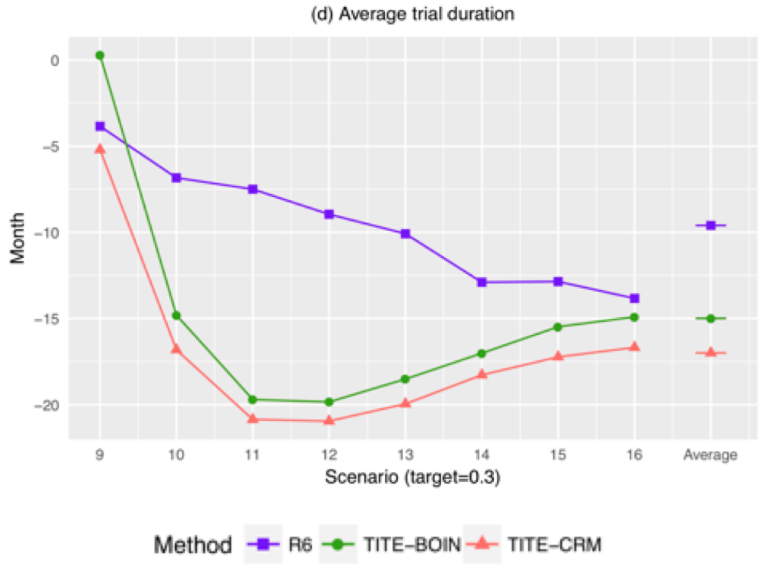


Percentage of patients overdosed

Select percentage above MTD



Trial duration



Summary

- By leveraging the follow-up time data from pending patients, TITE-BOIN is more efficient than rolling 6 design, and yields comparable accuracy to identify the MTD as TITE-CRM.
- TITE-BOIN is safer than TITE-CRM, and can be implemented in a simple and transparent way as rolling 6 design.
- TITE-BOIN has great potential to shorten the trial duration and accelerate drug development.

Application (protocol 2018-0899)

- Phase I study of a PARP inhibitor in combination with radiation therapy for recurrent gynecologic cancers
- DLT assessment window = 5 months
- 4 doses
- Target = 0.3
- Elicited prior toxicity probability in the trimesters of the assessment window (π_1, π_2, π_3)=(0.43, 0.46, 0.11)
- FDA protocol, IRB approved, ready to accrue

Decision table

Table 6. Dose escalation decision rules for large-field cohort

# of Treated Patients	# of Patients with DLTs	# of Patients with Pending Information	Decision Rule		
			Escalate	Stay	De-escalate
2	0	≤1	Y		
	0	2		Suspend accrual	
	≥1	≤1			Y
4	0	≤2	Y		
	0	≥3		Suspend accrual	
	1	0	Y		
	1	1	≥0.76	<0.76	
	1	2	≥1.84	<1.84	
	1	≥3		Suspend accrual	
	2	≤2			Y
	≥3	≤1			Y&Elim
6	0	≤3	Y		
	0	≥4		Suspend accrual	
	1	≤2	Y		
	1	3	≥1.4	<1.4	
	1	≥4		Suspend accrual	
	2	≤4			Y
	≥3	≤3			Y&Elim
	0	≤4	Y		
	0	≥5		Suspend accrual	

Application (protocol 2018-1129)

- Phase I study of BMS-986301 in advanced solid cancers
- 8 dose levels
- DLT assessment window = 28 days, but accrual is expected to be fast
- Accelerated titration + TITE-BOIN

Decision table

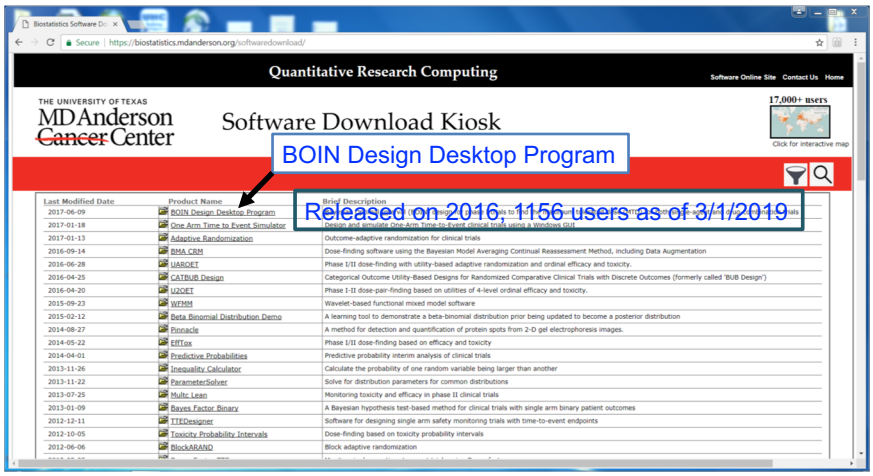
Table 1. Dose escalation/de-escalation rule for the TITE-BOIN design, pg. 1 of

No. treated	No. DLTs	No. data pending	STFT		
			Escalate	Stay	De-escalate
3	0	≤1	Y		
3	0	≥2		Suspend accrual	
3	1	0		Y	
3	1	1		>0.88	≤0.88
3	1	≥2		Suspend accrual	
3	2	≤1			Y
3	3	0			Y&Elim
6	0	≤3	Y		
6	0	≥4		Suspend accrual	
6	1	≤1	Y		
6	1	2	≥0.6	<0.6	
6	1	3	≥1.96	<1.96	
6	1	≥4		Suspend accrual	

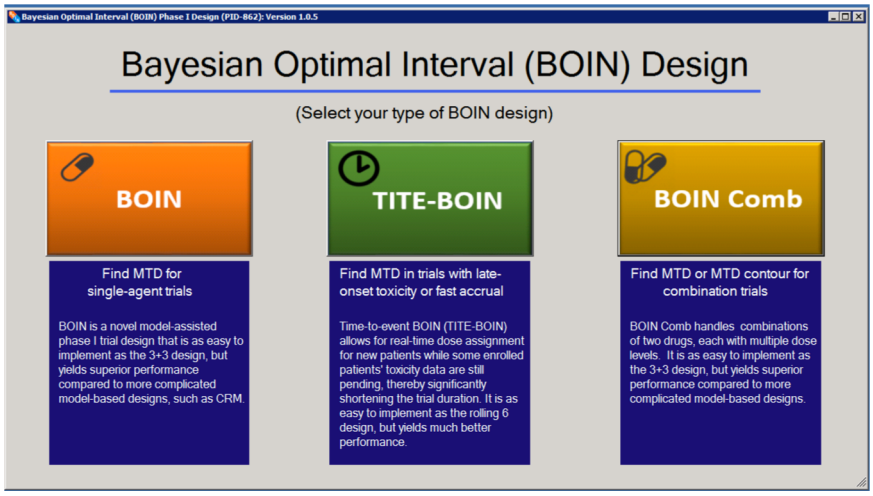
Software

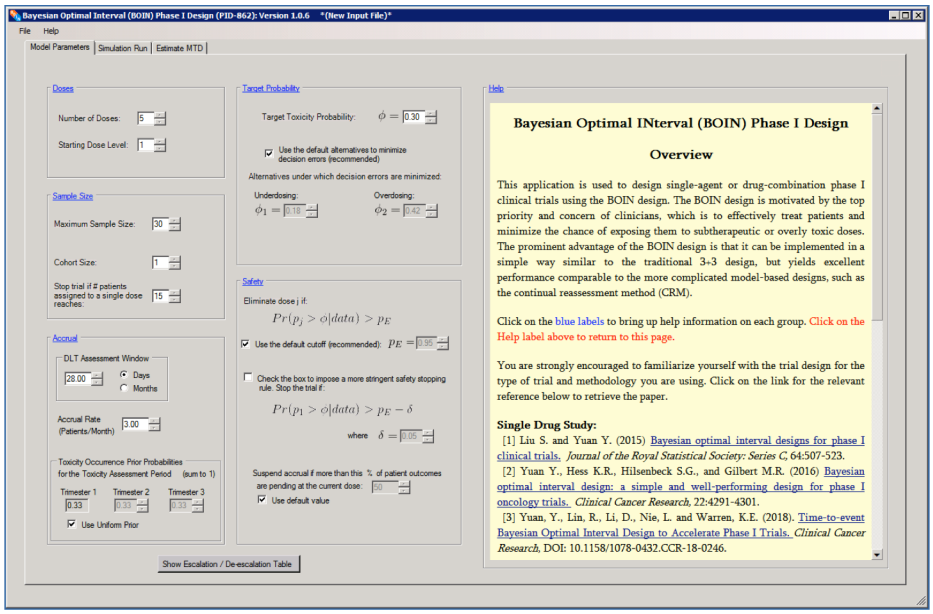
- Windows desktop program for TITE-BOIN is freely available at the MD Anderson Software Download Website https://biostatistics.mdanderson.org/softwaredownload/SingleSoftware.aspx?Software_Id=81.
- Web applications for TITE-BOIN is freely available at http://www.trialdesign.org.

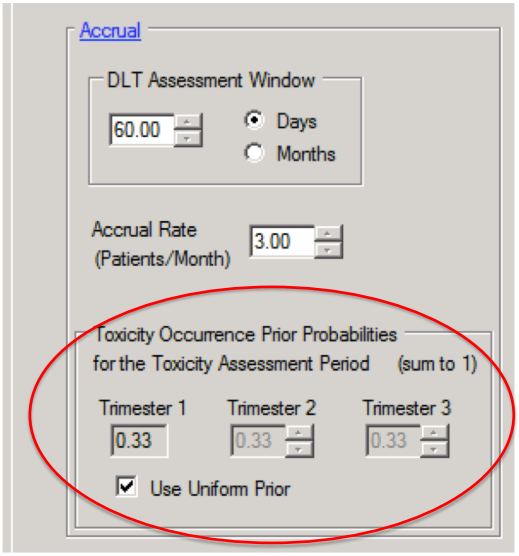
BOIN desktop program

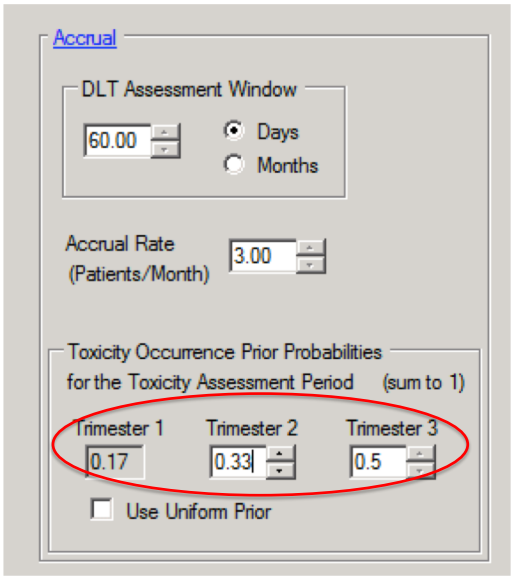


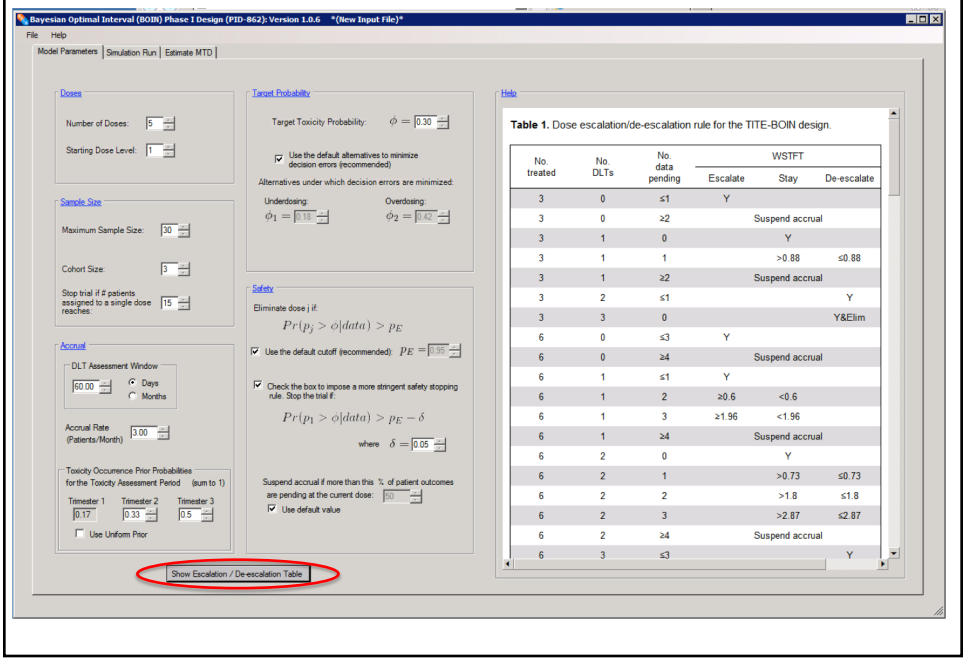
Software

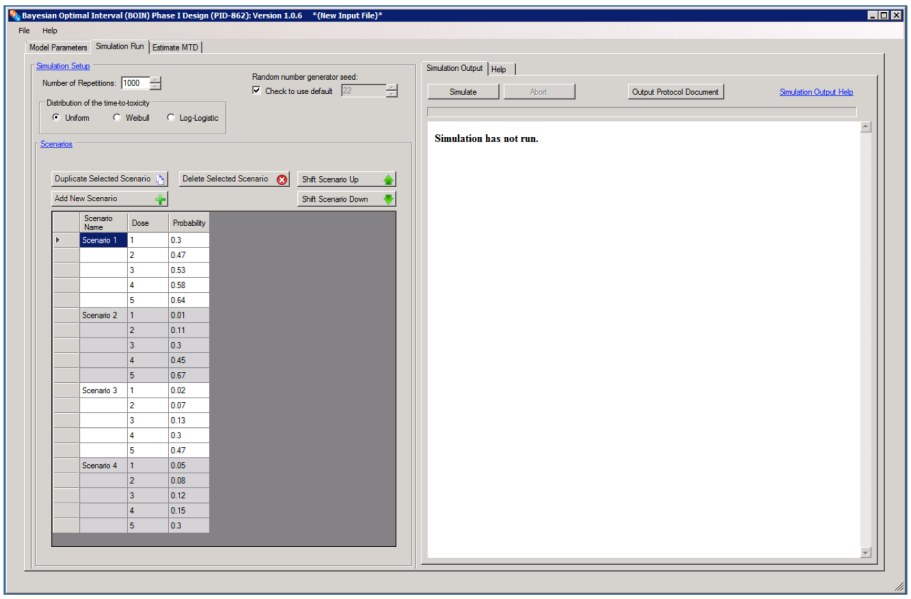


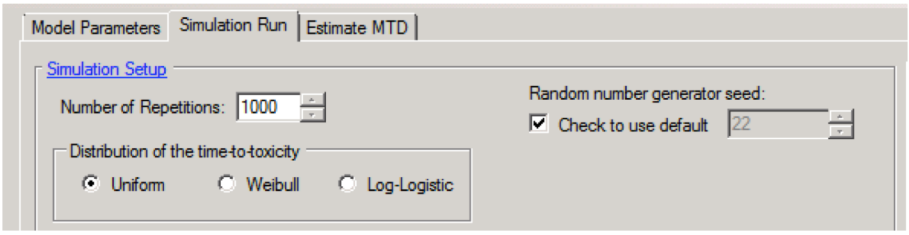

Bayesian Optimal Interval (BOIN) Phase I Design (PID-862): Version 1.0.6 *(New Input File)*
File Help
Model Parameters | Simulation Run | Estimate MTD
Doses
Number of Doses: 5
Starting Dose Level: 1
Sample Size
Maximum Sample Size: 30
Cohort Size: 1
Stop trial if # patients assigned to a single dose reaches: 15
Accrual
DLT Assessment Window
28.00 Days Months
Accrual Rate (Patients/Month) 3.00
Toxicity Occurrence Prior Probabilities for the Toxicity Assessment Period (sum to 1)
Trimester 1 Trimester 2 Trimester 3
0.33 0.33 0.33
Use Uniform Prior
Target Probability
Target Toxicity Probability: $\phi = 0.30$
Use the default alternatives to minimize decision errors (recommended)
Alternatives under which decision errors are minimized:
Underdosing: $\phi_1 = 0.18$
Overdosing: $\phi_2 = 0.42$
Safety
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. Stop the trial if:
$Pr(p_1 > \phi|data) > p_E - \delta$
where $\delta = 0.05$
Suspend accrual if more than this % of patient outcomes are pending at the current dose: 90
Use default value
Show Escalation / De-escalation Table
Help
Bayesian Optimal INterval (BOIN) Phase I Design
Overview
This application is used to design single-agent or drug-combination phase I clinical trials using the BOIN design. The BOIN design is motivated by the top priority and concern of clinicians, which is to effectively treat patients and minimize the chance of exposing them to subtherapeutic or overly toxic doses. The prominent advantage of the BOIN design is that it can be implemented in a simple way similar to the traditional 3+3 design, but yields excellent performance comparable to the more complicated model-based designs, such as the continual reassessment method (CRM).
Click on the blue labels to bring up help information on each group. Click on the Help label above to return to this page.
You are strongly encouraged to familiarize yourself with the trial design for the type of trial and methodology you are using. Click on the link for the relevant reference below to retrieve the paper.
Single Drug Study:
[1] 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.
[2] 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.
[3] Yuan, Y., Lin, R., Li, D., Nie, L. and Warren, K.E. (2018). Time-to-event Bayesian Optimal Interval Design to Accelerate Phase I Trials. Clinical Cancer Research, DOI: 10.1158/1078-0432.CCR-18-0246.

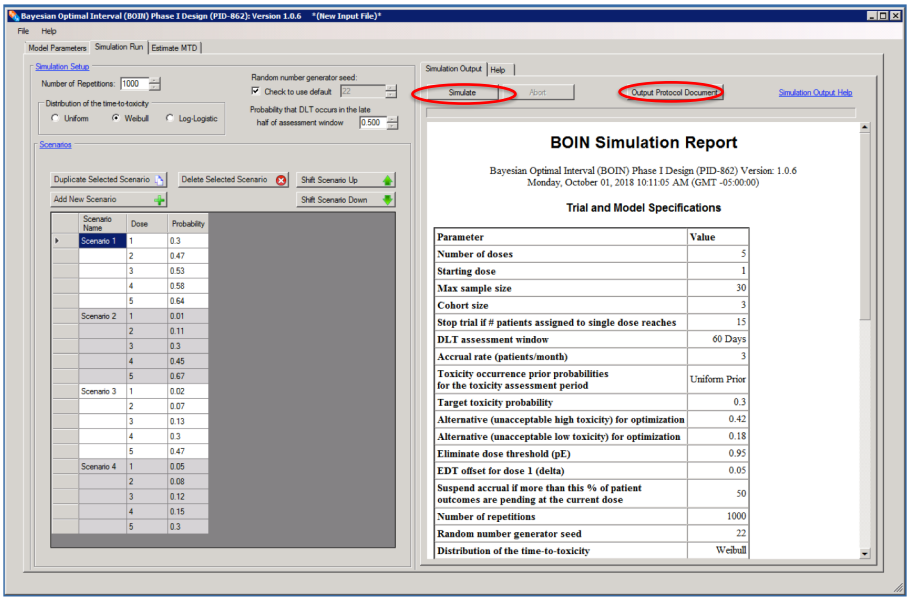

Accrual
DLT Assessment Window
60.00
Days
Months
Accrual Rate
(Patients/Month)
3.00
Toxicity Occurrence Prior Probabilities
for the Toxicity Assessment Period (sum to 1)
Trimester 1
Trimester 2
Trimester 3
0.33
0.33
0.33
Use Uniform Prior

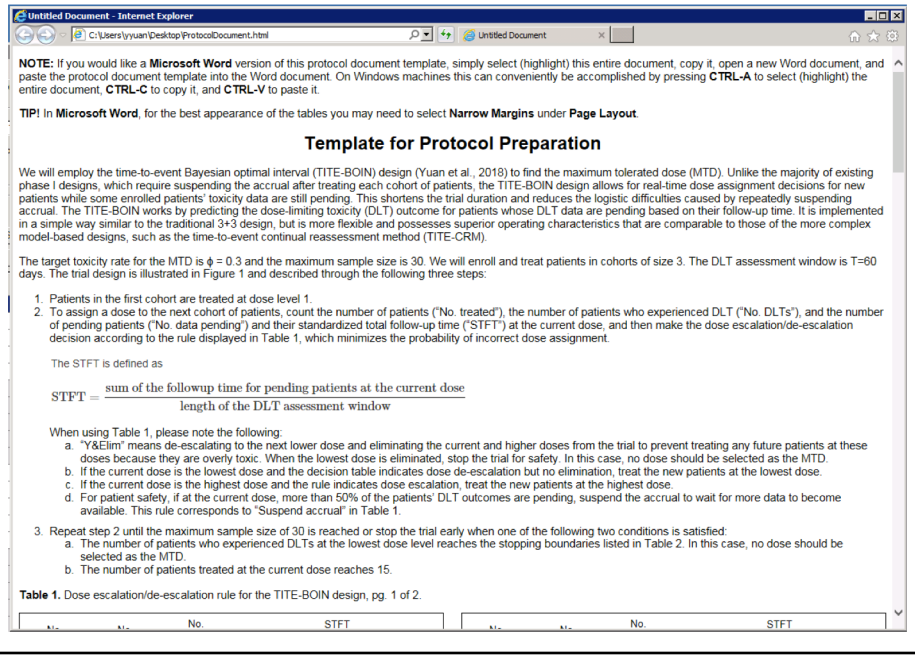

Accrual
DLT Assessment Window
60.00
Days
Months
Accrual Rate
(Patients/Month)
3.00
Toxicity Occurrence Prior Probabilities
for the Toxicity Assessment Period (sum to 1)
Trimester 1
Trimester 2
Trimester 3
0.17
0.33
0.5
Use Uniform Prior


Bayesian Optimal Interval (BOIN) Phase I Design (PID-862): Version 1.0.6 *(New Input File)*
File Help
Model Parameters | Simulation Run | Estimate MTD
Doses
Number of Doses: 5
Starting Dose Level: 1
Sample Size
Maximum Sample Size: 30
Cohort Size: 3
Stop trial if # patients assigned to a single dose reaches: 15
Accrual
DLT Assessment Window
60.00 Days Months
Accrual Rate (Patients/Month) 3.00
Toxicity Occurrence Prior Probabilities for the Toxicity Assessment Period (sum to 1)
Trimester 1 0.17
Trimester 2 0.33
Trimester 3 0.5
Use Uniform Prior
Target Probability
Target Toxicity Probability: $\phi = 0.30$
Use the default alternatives to minimize decision errors (recommended)
Alternatives under which decision errors are minimized:
Underdosing: $\phi_1 = 0.18$
Overdosing: $\phi_2 = 0.42$
Safety
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. Stop the trial if:
$Pr(p_1 > \phi|data) > p_E - \delta$
where $\delta = 0.05$
Suspend accrual if more than this % of patient outcomes are pending at the current dose: 50
Use default value
Show Escalation / De-escalation Table
Help
Table 1. Dose escalation/de-escalation rule for the TITE-BOIN design.
No. treated | No. DLTs | No. data pending | WSTFT: Escalate | Stay | De-escalate
3 | 0 | ≤1 | Y | | |
3 | 0 | ≥2 | | Suspend accrual | |
3 | 1 | 0 | | Y | |
3 | 1 | 1 | | >0.88 | ≤0.88
3 | 1 | ≥2 | | Suspend accrual | |
3 | 2 | ≤1 | | | Y
3 | 3 | 0 | | | Y&Elim
6 | 0 | ≤3 | Y | | |
6 | 0 | ≥4 | | Suspend accrual | |
6 | 1 | ≤1 | Y | | |
6 | 1 | 2 | ≥0.6 | <0.6 | |
6 | 1 | 3 | ≥1.96 | <1.96 | |
6 | 1 | ≥4 | | Suspend accrual | |
6 | 2 | 0 | | Y | |
6 | 2 | 1 | | >0.73 | ≤0.73
6 | 2 | 2 | | >1.8 | ≤1.8
6 | 2 | 3 | | >2.87 | ≤2.87
6 | 2 | ≥4 | | Suspend accrual | |
6 | 3 | ≤3 | | | Y


Bayesian Optimal Interval (BOIN) Phase I Design (PID-862): Version 1.0.6 *(New Input File)*
File Help
Model Parameters Simulation Run Estimate MTD
Simulation Setup
Number of Repetitions: 1000
Random number generator seed:
Check to use default 22
Distribution of the time-to-toxicity
Uniform Weibull Log-Logistic
Scenarios
Duplicate Selected Scenario
Delete Selected Scenario
Shift Scenario Up
Add New Scenario
Shift Scenario Down
Scenario Name Dose Probability
Scenario 1 1 0.3
2 0.47
3 0.53
4 0.58
5 0.64
Scenario 2 1 0.01
2 0.11
3 0.3
4 0.45
5 0.67
Scenario 3 1 0.02
2 0.07
3 0.13
4 0.3
5 0.47
Scenario 4 1 0.05
2 0.08
3 0.12
4 0.15
5 0.3
Simulation Output Help
Simulate Abort
Output Protocol Document
Simulation Output Help
Simulation has not run.


Model Parameters
Simulation Run
Estimate MTD
Simulation Setup
Number of Repetitions: 1000
Random number generator seed:
Check to use default 22
Distribution of the time-to-toxicity
Uniform Weibull Log-Logistic


Bayesian Optimal Interval (BOIN) Phase I Design (PID-862): Version 1.0.6 *(New Input File)*
File Help
Model Parameters Simulation Run Estimate MTD
Simulation Setup
Number of Repetitions: 1000
Random number generator seed:
Check to use default 22
Distribution of the time-to-toxicity
Uniform Weibull Log-Logistic
Probability that DLT occurs in the late half of assessment window 0.500
Scenarios
Duplicate Selected Scenario
Delete Selected Scenario
Shift Scenario Up
Add New Scenario
Shift Scenario Down
Scenario Name Dose Probability
Scenario 1 1 0.3
2 0.47
3 0.53
4 0.58
5 0.64
Scenario 2 1 0.01
2 0.11
3 0.3
4 0.45
5 0.67
Scenario 3 1 0.02
2 0.07
3 0.13
4 0.3
5 0.47
Scenario 4 1 0.05
2 0.08
3 0.12
4 0.15
5 0.3
Simulation Output Help
Simulate
Abort
Output Protocol Document
Simulation Output Help
BOIN Simulation Report
Bayesian Optimal Interval (BOIN) Phase I Design (PID-862) Version: 1.0.6
Monday, October 01, 2018 10:11:05 AM (GMT -05:00:00)
Trial and Model Specifications
Parameter Value
Number of doses 5
Starting dose 1
Max sample size 30
Cohort size 3
Stop trial if # patients assigned to single dose reaches 15
DLT assessment window 60 Days
Accrual rate (patients/month) 3
Toxicity occurrence prior probabilities for the toxicity assessment period Uniform Prior
Target toxicity probability 0.3
Alternative (unacceptable high toxicity) for optimization 0.42
Alternative (unacceptable low toxicity) for optimization 0.18
Eliminate dose threshold (pE) 0.95
EDT offset for dose 1 (delta) 0.05
Suspend accrual if more than this % of patient outcomes are pending at the current dose 50
Number of repetitions 1000
Random number generator seed 22
Distribution of the time-to-toxicity Weibull


Untitled Document - Internet Explorer
C:\Users\yyuan\Desktop\ProtocolDocument.html
Untitled Document
NOTE: If you would like a Microsoft Word version of this protocol document template, simply select (highlight) this entire document, copy it, open a new Word document, and paste the protocol document template into the Word document. On Windows machines this can conveniently be accomplished by pressing CTRL-A to select (highlight) the entire document, CTRL-C to copy it, and CTRL-V to paste it.
TIP! In Microsoft Word, for the best appearance of the tables you may need to select Narrow Margins under Page Layout.
Template for Protocol Preparation
We will employ the time-to-event Bayesian optimal interval (TITE-BOIN) design (Yuan et al., 2018) to find the maximum tolerated dose (MTD). Unlike the majority of existing phase I designs, which require suspending the accrual after treating each cohort of patients, the TITE-BOIN design allows for real-time dose assignment decisions for new patients while some enrolled patients' toxicity data are still pending. This shortens the trial duration and reduces the logistic difficulties caused by repeatedly suspending accrual. The TITE-BOIN works by predicting the dose-limiting toxicity (DLT) outcome for patients whose DLT data are pending based on their follow-up time. It is implemented in a simple way similar to the traditional 3+3 design, but is more flexible and possesses superior operating characteristics that are comparable to those of the more complex model-based designs, such as the time-to-event continual reassessment method (TITE-CRM).
The target toxicity rate for the MTD is ϕ = 0.3 and the maximum sample size is 30. We will enroll and treat patients in cohorts of size 3. The DLT assessment window is T=60 days. The trial design is illustrated in Figure 1 and described through the following three steps:
1. Patients in the first cohort are treated at dose level 1.
2. To assign a dose to the next cohort of patients, count the number of patients ("No. treated"), the number of patients who experienced DLT ("No. DLTs"), and the number of pending patients ("No. data pending") and their standardized total follow-up time ("STFT") at the current dose, and then make the dose escalation/de-escalation decision according to the rule displayed in Table 1, which minimizes the probability of incorrect dose assignment.
The STFT is defined as
STFT = sum of the followup time for pending patients at the current dose / length of the DLT assessment window
When using Table 1, please note the following:
a. "Y&Elim" means de-escalating to the next lower dose and eliminating the current and higher doses from the trial to prevent treating any future patients at these doses because they are overly toxic. When the lowest dose is eliminated, stop the trial for safety. In this case, no dose should be selected as the MTD.
b. If the current dose is the lowest dose and the decision table indicates dose de-escalation but no elimination, treat the new patients at the lowest dose.
c. If the current dose is the highest dose and the rule indicates dose escalation, treat the new patients at the highest dose.
d. For patient safety, if at the current dose, more than 50% of the patients' DLT outcomes are pending, suspend the accrual to wait for more data to become available. This rule corresponds to "Suspend accrual" in Table 1.
3. Repeat step 2 until the maximum sample size of 30 is reached or stop the trial early when one of the following two conditions is satisfied:
a. The number of patients who experienced DLTs at the lowest dose level reaches the stopping boundaries listed in Table 2. In this case, no dose should be selected as the MTD.
b. The number of patients treated at the current dose reaches 15.
Table 1. Dose escalation/de-escalation rule for the TITE-BOIN design, pg. 1 of 2.
No. STFT
No. STFT

Untitled Document - Internet Explorer

C:\Users\yyuan\Desktop\ProtocolDocument.html

Untitled Document

b. The number of patients treated at the current dose reaches 15.

Table 1. Dose escalation/de-escalation rule for the TITE-BOIN design, pg. 1 of 2.

No. treated	No. DLTs	No. data pending	STFT		
			Escalate	Stay	De-escalate
3	0	≤1	Y		
3	0	≥2		Suspend accrual	
3	1	0		Y	
3	1	1		>0.88	≤0.88
3	1	≥2		Suspend accrual	
3	2	≤1			Y
3	3	0			Y&Elim
6	0	≤3	Y		
6	0	≥4		Suspend accrual	
6	1	≤1	Y		
6	1	2	≥0.6	<0.6	
6	1	3	≥1.96	<1.96	
6	1	≥4		Suspend accrual	
6	2	0		Y	
6	2	1		>0.73	≤0.73
6	2	2		>1.8	≤1.8
6	2	3		>2.87	≤2.87
6	2	≥4		Suspend accrual	
6	3	≤3			Y
6	≥4	≤2			Y&Elim
9	0	≤4	Y		
9	0	≥5		Suspend accrual	

No. treated	No. DLTs	No. data pending	STFT		
			Escalate	Stay	De-escalate
9	1	≤4	Y		
9	1	≥5		Suspend accrual	
9	2	0	Y		
9	2	1	≥0.59	<0.59	
9	2	2	≥1.65	<1.65	
9	2	3	≥2.71	<2.71	
9	2	4	≥3.77	<3.77	
9	2	≥5		Suspend accrual	
9	3	0		Y	
9	3	1		>0.58	≤0.58
9	3	2		>1.65	≤1.65
9	3	3		>2.72	≤2.72
9	3	4		>3.79	≤3.79
9	3	≥5		Suspend accrual	
9	4	≤5			Y
9	≥5	≤4			Y&Elim
12	0	≤6	Y		
12	0	≥7		Suspend accrual	
12	1	≤6	Y		
12	1	≥7		Suspend accrual	
12	2	≤3	Y		
12	2	4	≥1.33	<1.33	

Table 1. Dose escalation/de-escalation rule for the TITE-BOIN design, cont., pg. 2 of 2.

Untitled Document - Internet Explorer

C:\Users\yyuan\Desktop\ProtocolDocument.html

Untitled Document

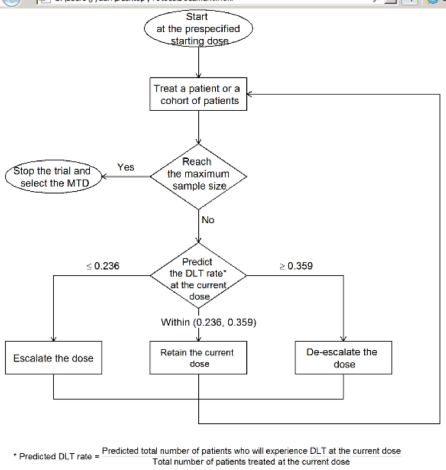
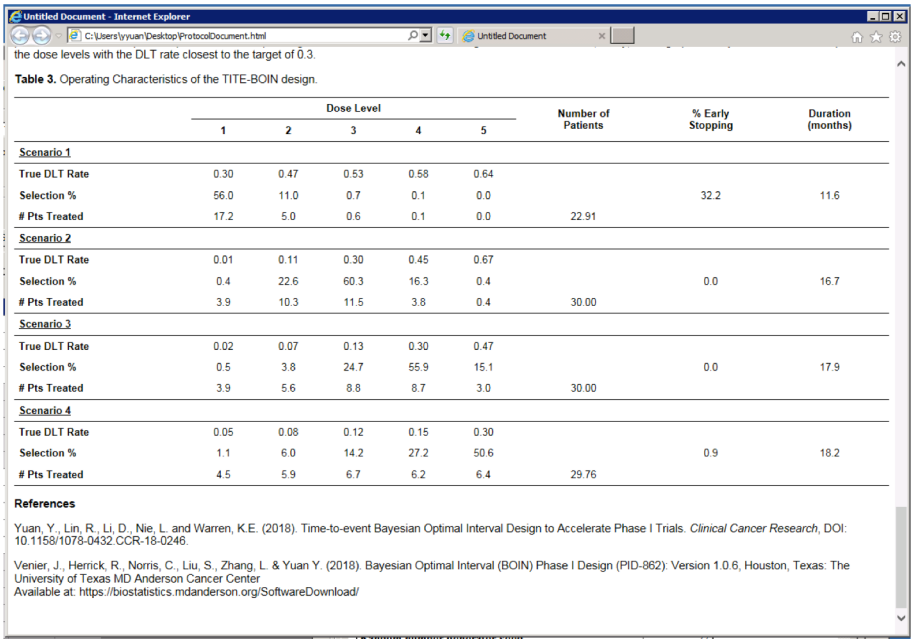


Figure 1. Flowchart for trial conduct using the BOIN design.

After the trial is completed, select the MTD based on isotonic regression as specified in Yuan et al. (2018). This computation is implemented by the "Estimate MTD" tab of the BOIN Design Desktop Program (Venier et al., 2018). Specifically, select as the MTD the dose for which the isotonic estimate of the toxicity rate is closest to the target toxicity rate. If there are ties, select the higher dose level when the isotonic estimate is lower than the target toxicity rate and select the lower dose level when the isotonic estimate is greater than or equal to the target toxicity rate.

Optional:[In case there is cohort expansion after identifying the MTD] Once we determine the MTD, an additional *n* patients will be enrolled for additional experience with



the dose levels with the DLT rate closest to the target of 0.3.

Table 3. Operating Characteristics of the TITE-BOIN design.

	Dose Level					Number of Patients	% Early Stopping	Duration (months)
	1	2	3	4	5			
Scenario 1								
True DLT Rate	0.30	0.47	0.53	0.58	0.64			
Selection %	56.0	11.0	0.7	0.1	0.0		32.2	11.6
# Pts Treated	17.2	5.0	0.6	0.1	0.0	22.91		
Scenario 2								
True DLT Rate	0.01	0.11	0.30	0.45	0.67			
Selection %	0.4	22.6	60.3	16.3	0.4		0.0	16.7
# Pts Treated	3.9	10.3	11.5	3.8	0.4	30.00		
Scenario 3								
True DLT Rate	0.02	0.07	0.13	0.30	0.47			
Selection %	0.5	3.8	24.7	55.9	15.1		0.0	17.9
# Pts Treated	3.9	5.6	8.8	8.7	3.0	30.00		
Scenario 4								
True DLT Rate	0.05	0.08	0.12	0.15	0.30			
Selection %	1.1	6.0	14.2	27.2	50.6		0.9	18.2
# Pts Treated	4.5	5.9	6.7	6.2	6.4	29.76		

References

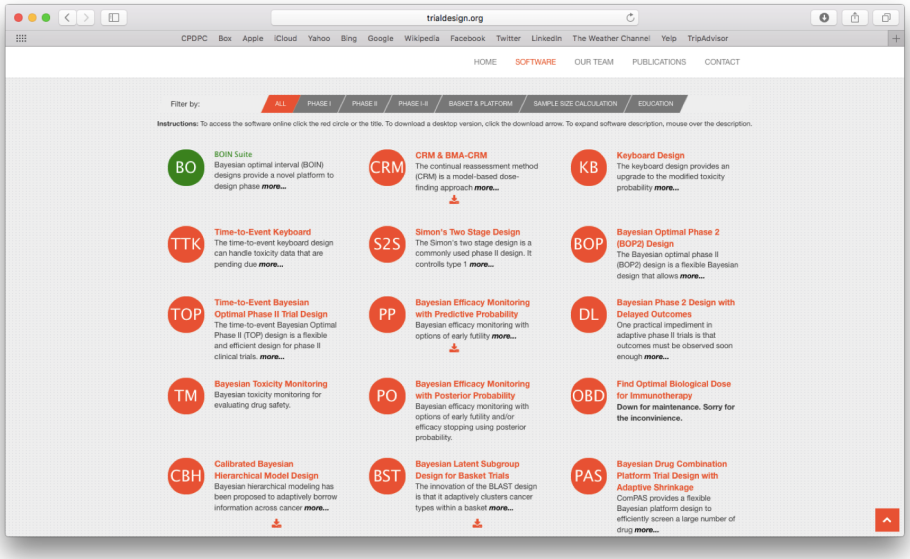
Yuan, Y., Lin, R., Li, D., Nie, L. and Warren, K.E. (2018). Time-to-event Bayesian Optimal Interval Design to Accelerate Phase I Trials. *Clinical Cancer Research*, DOI: 10.1158/1078-0432.CCR-18-0246.

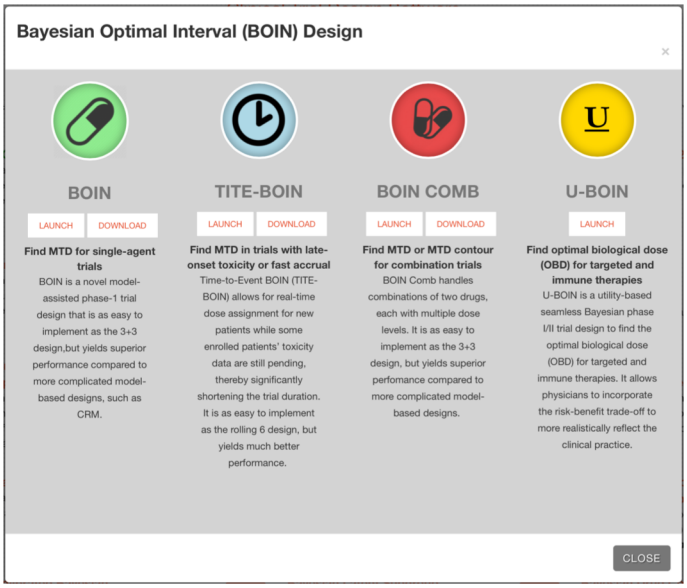
Venier, J., Herrick, R., Norris, C., Liu, S., Zhang, L. & Yuan Y. (2018). Bayesian Optimal Interval (BOIN) Phase I Design (PID-862): Version 1.0.6, Houston, Texas: The University of Texas MD Anderson Cancer Center
Available at: https://biostatistics.mdanderson.org/SoftwareDownload/

Anything better?

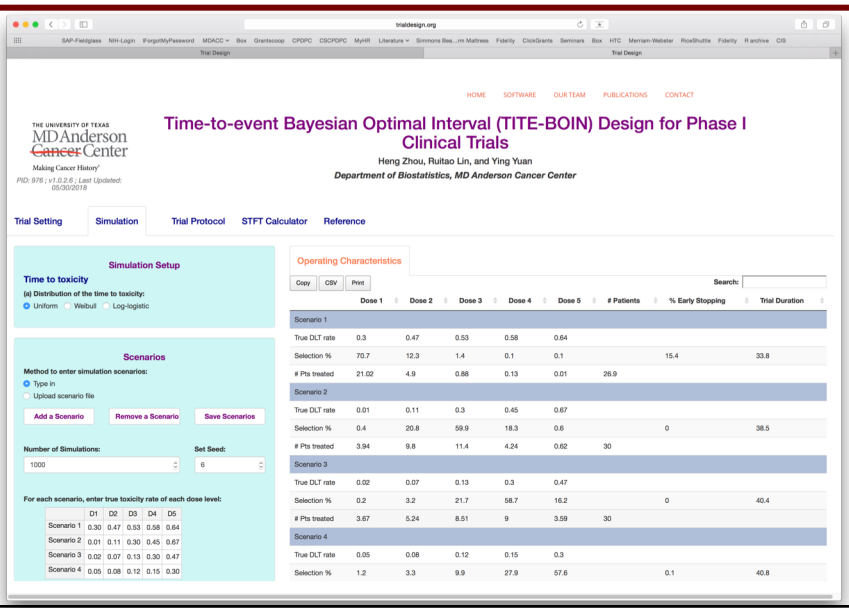
www.trialdesign.org

www.trialdesign.org

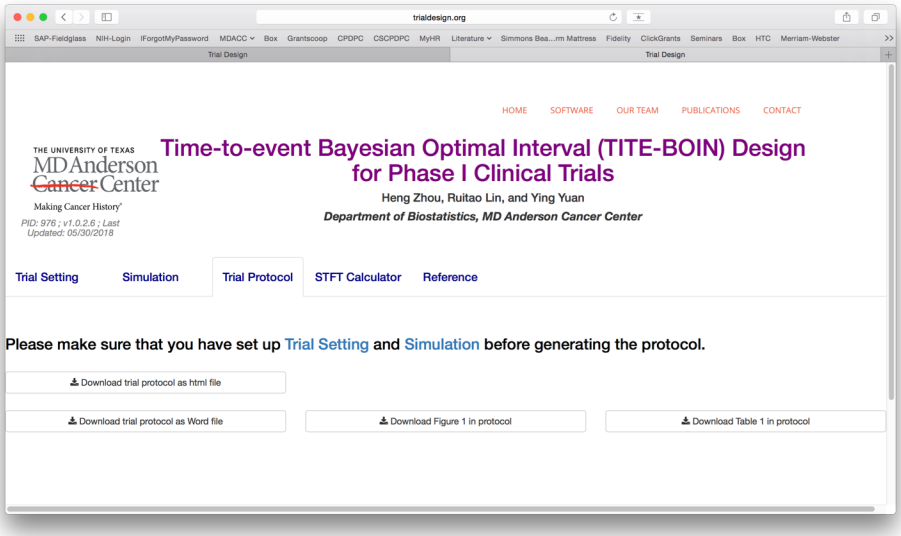




www.trialdesign.org



www.trialdesign.org



References

- Zhou H, Yuan Y and Nie L (2018) Accuracy, safety and reliability of novel Bayesian phase I trial designs. *Clinical Cancer Research*, 24(18):4357-4364
- Yuan Y, Lin R, Li D, Nie L and Warren KE (2018) Time-to-event Bayesian optimal interval design to accelerate phase I trials, *Clinical Cancer Research*, 24, 4921-4930.
- Lin R and Yuan Y (2019) Time-to-event model-assisted designs for dose-finding trials with delayed toxicity, *Biostatistics*, in press
  (discussed TITE-keyboard design and TITE-mTPI design)