BOIN: A Novel Platform for Designing Early Phase Clinical Trials

Ying Yuan
Professor
Co-chief of Section of Adaptive Design
MD Anderson Cancer Center

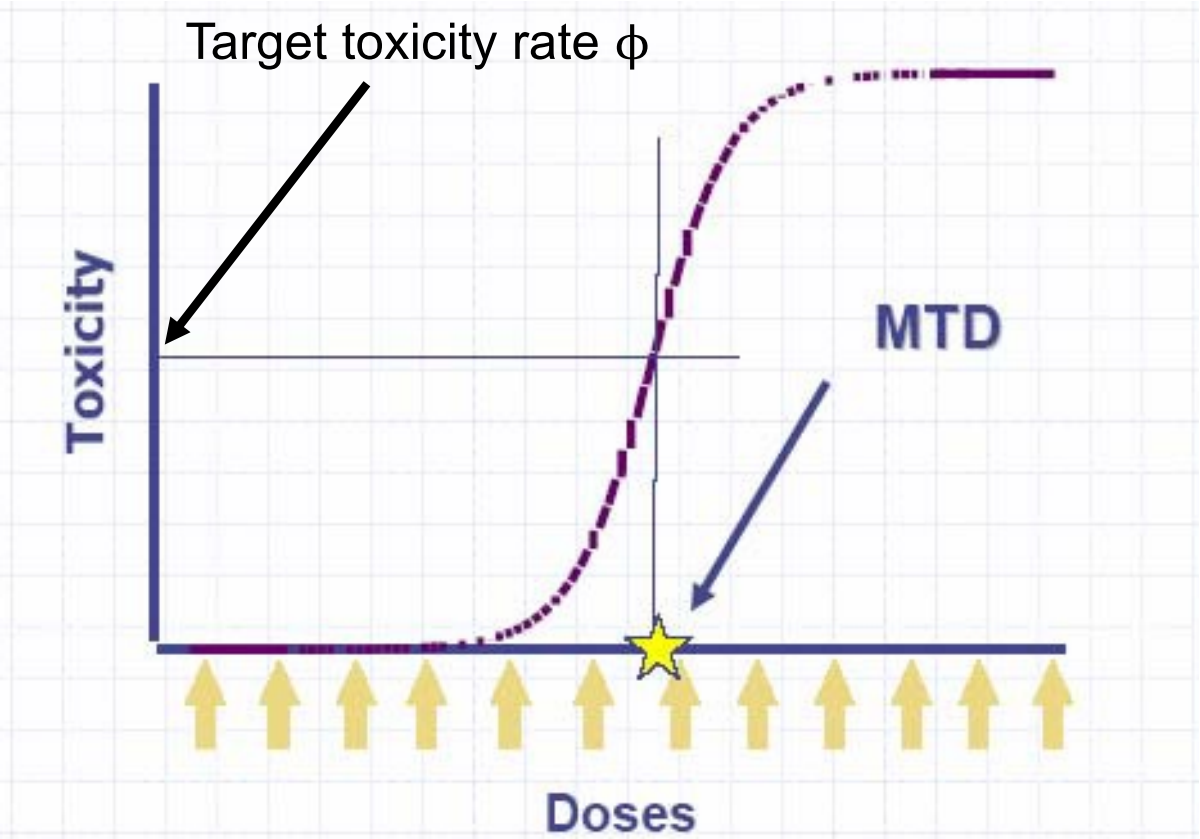
THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Outline

- Overview of phase I trial designs
- Bayesian optimal interval (BOIN) platform
  - Single-agent trials
  - Drug-combination trials
  - Late-onset toxicity/fast accrual
- Software

Phase I Clinical Trials

- The objective of phase I clinical trials is to find the maximum tolerated dose (MTD) that has a target toxicity probability of ϕ.



Three Types of Phase I Designs

- **Algorithm-based designs**
  - Dose transition is based on a prespecified algorithm.
  - Example: 3+3 design
  - Transparent, easy to implement, but poor performance.
- **Model-based designs**
  - A dose-toxicity model is assumed, and the updated based on the accrued data to guide the dose transition.
  - Example: CRM (O'Quigley et al. 1990), EWOC (Babb et al., 1998), BLRM (Neuenschwander et al., 2008)
  - Superior performance, but less transparent and difficult to implement.
- **Model-assisted designs**
  - A class of designs that utilize a model for efficient decision making, similar to the model-based design, but its rule of dose escalation/deescalationcan be predetermined before the onset of the trial in a fashion similar to the algorithm-based design (Yan, Mandrekar and Yuan, 2017).
  - Examples: BOIN (Liu and Yuan, 2015), and keyboard design (Yan, Mandrekar and Yuan, 2017).
  - Transparent and easy to implement with superior performance

Three Types of Designs

- **Algorithm-based designs**
  - Dose transition is based on a prespecified algorithm.
  - Example: 3+3 design
  - Transparent and easy to implement, but poor performance.
- **Model-based designs**
  - A dose-toxicity model is assumed, and the updated based on the accrued data to guide the dose transition.
  - Example: CRM (O'Quigley et al. 1990), EWOC (Babb et al., 1998), BLRM (Neuenschwander et al., 2008)
  - Superior performance, but less transparent and difficult to implement.
- **Model-assisted designs**
  - A class of designs that utilize a model for efficient decision making, similar to the model-based design, but its rule of dose escalation/deescalationcan be predetermined before the onset of the trial in a fashion similar to the algorithm-based design (Yan, Mandrekar and Yuan, 2017).
  - Examples: BOIN (Liu and Yuan, 2015), and keyboard design (Yan, Mandrekar and Yuan, 2017).
  - Transparent and easy to implement with superior performance

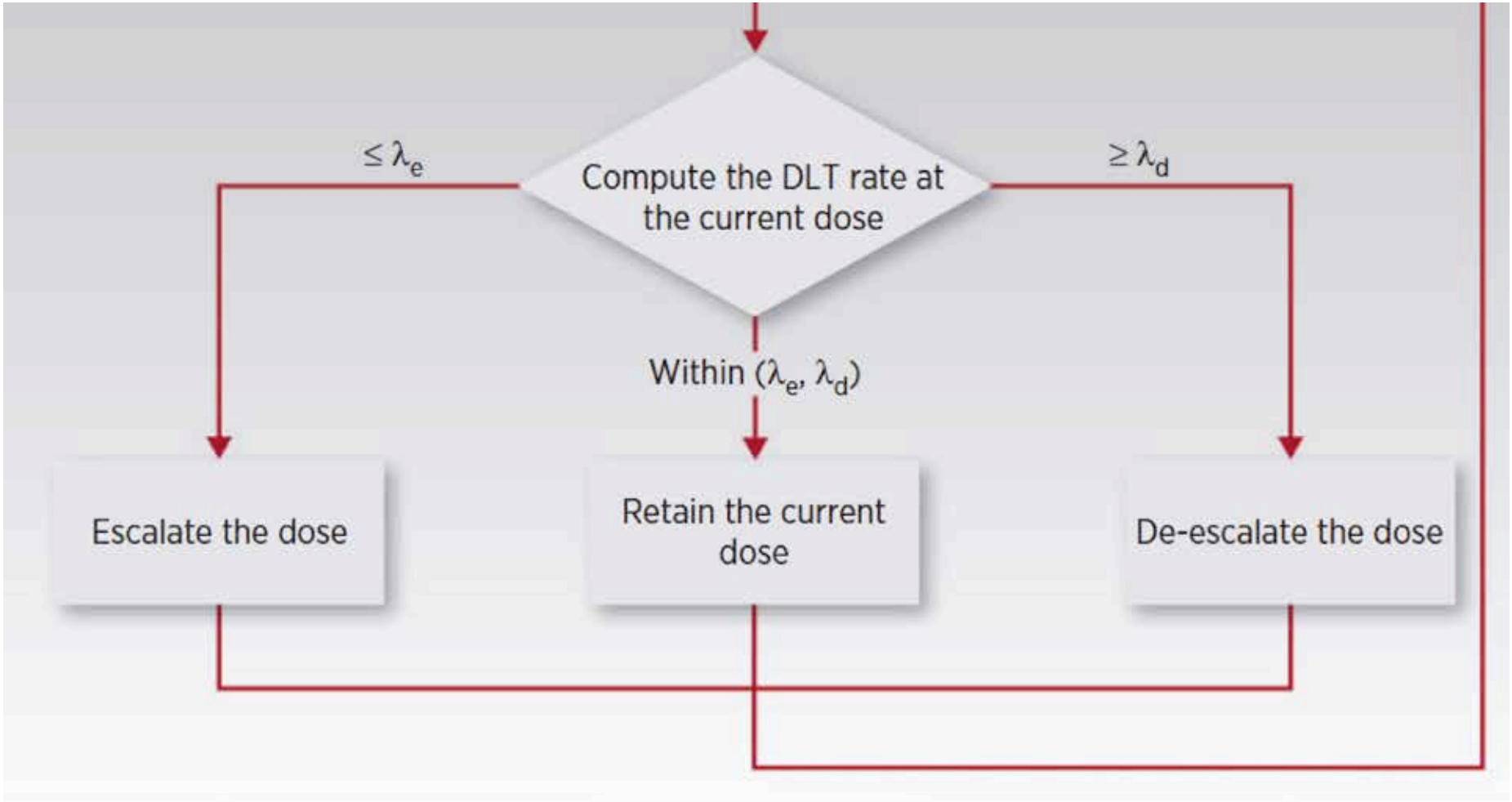
Three Types of Designs

- **Algorithm-based designs**
  - Dose transition is based on a prespecified algorithm.
  - Example: 3+3 design
  - Transparent, easy to implement, but perform poorly.
- **Model-based designs**
  - A dose-toxicity model is assumed and updated based on the accrued data to guide the dose transition.
  - Example: CRM (O'Quigley et al. 1990), EWOC (Babb et al., 1998), BLRM (Neuenschwander et al., 2008)
  - Superior performance, but less transparent and difficult to implement.
- **Model-assisted designs**
  - A class of designs that utilize a model for efficient decision making, similar to the model-based design, but its rule of dose escalation/deescalationcan be predetermined before the onset of the trial in a fashion similar to the algorithm-based design (Yan, Mandrekar and Yuan, 2017).
  - Examples: BOIN (Liu and Yuan, 2015), and keyboard design (Yan, Mandrekar and Yuan, 2017).
  - Transparent and easy to implement with superior performance

Three Types of Designs

- **Algorithm-based designs**
  - Dose transition is based on a prespecified algorithm.
  - Example: 3+3 design
  - Transparent, easy to implement, but perform poorly.
- **Model-based designs**
  - A dose-toxicity model is assumed, and the updated based on accrued data to guide the dose transition.
  - Example: CRM (O'Quigley et al. 1990), EWOC (Babb et al., 1998), BLRM (Neuenschwander et al., 2008)
  - Good performance, but less transparent and difficult to implement.
- **Model-assisted designs (Yan et al., 2017, Zhou et al., 2018)**
  - A class of designs that utilize a model for efficient decision making, similar to the model-based design, but its dose escalation/de-escalation rule can be predetermined before the onset of the trial in a fashion similar to the algorithm-based design (Yan, Mandrekar and Yuan, 2017).
  - Easy to implement + superior performance.
  - Examples: mTPI (Ji et al, 2008), BOIN (Liu and Yuan, 2015), Keyboard design (Yan, et al., 2017).

Bayesian Optimal Interval (BOIN) Design



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

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

Note: 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

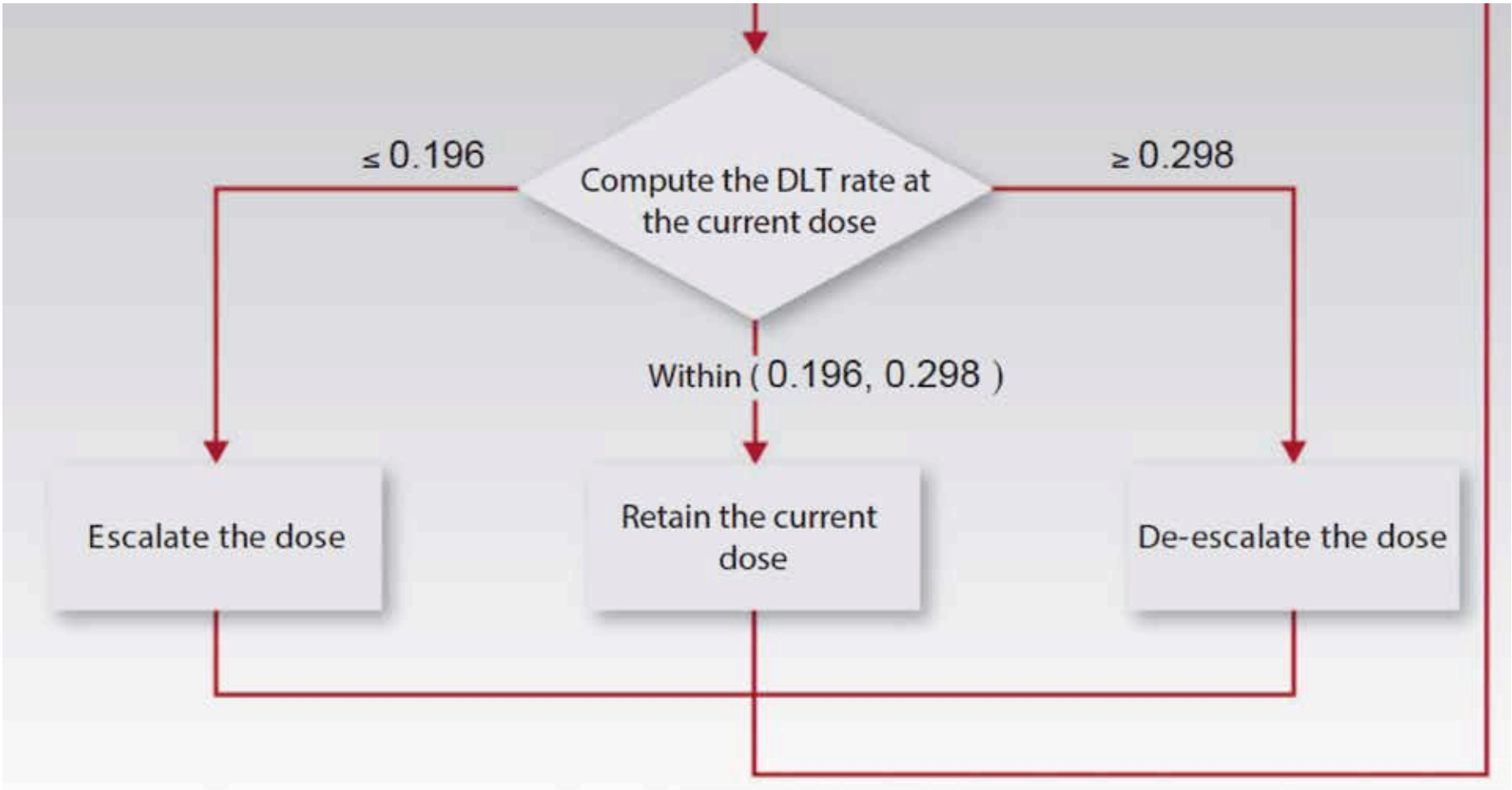
Table 1. Dose escalation and de-escalation boundaries

	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

Note: 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 for Target = 25%



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

Conduct of Phase I Trials

- Start the trial by treating the first cohort of patient(s) at the lowest or prespecified starting dose level
- Then

Three possible decisions:

- Escalate the dose
- Deescalate the dose
- Retain the current dose

Conduct of Phase I Trials

- If we knew the true toxicity rate of the current dose j (i.e., p_j), decision is easy:
  - Escalate the dose if $p_j < \phi$
  - Deescalate the dose if $p_j > \phi$
  - Retain the current dose if $p_j = \phi$

Conduct of Phase I Trials

- Then

- Escalate the dose if $p_j < \phi$
- Deescalate the dose if $p_j > \phi$
- Retain the current dose if $p_j = \phi$

……

- Repeated the above step of dose assignment until the trial is completed

Oracle Design

- Phase I trials can be viewed as a sequence of adaptive decision-making steps of dose assignment for patient who are sequentially enrolled into the trial
- If p_j was known, we obtain the oracle design
  - No decision error
  - Optimal dosing for each patient

Optimize Adaptive Decision

- In reality, the oracle design does not exist
- Decisions must be made adaptively based on the observed data
- How to make optimal adaptive decisions?
  - Minimize the chance of incorrect decisions so that the resulting design gets as close as possible to the oracle design
- The solution is the BOIN design

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.

Notation

- *J* doses are under investigation
- ϕ is the target dose-limiting toxicity (DLT) rate
- p_j denotes the true DLT rate for dose level j
- $\hat{p}_j$ denotes the observed DLT rate at dose level j at an interim decision time

A Class of Nonparametric Designs

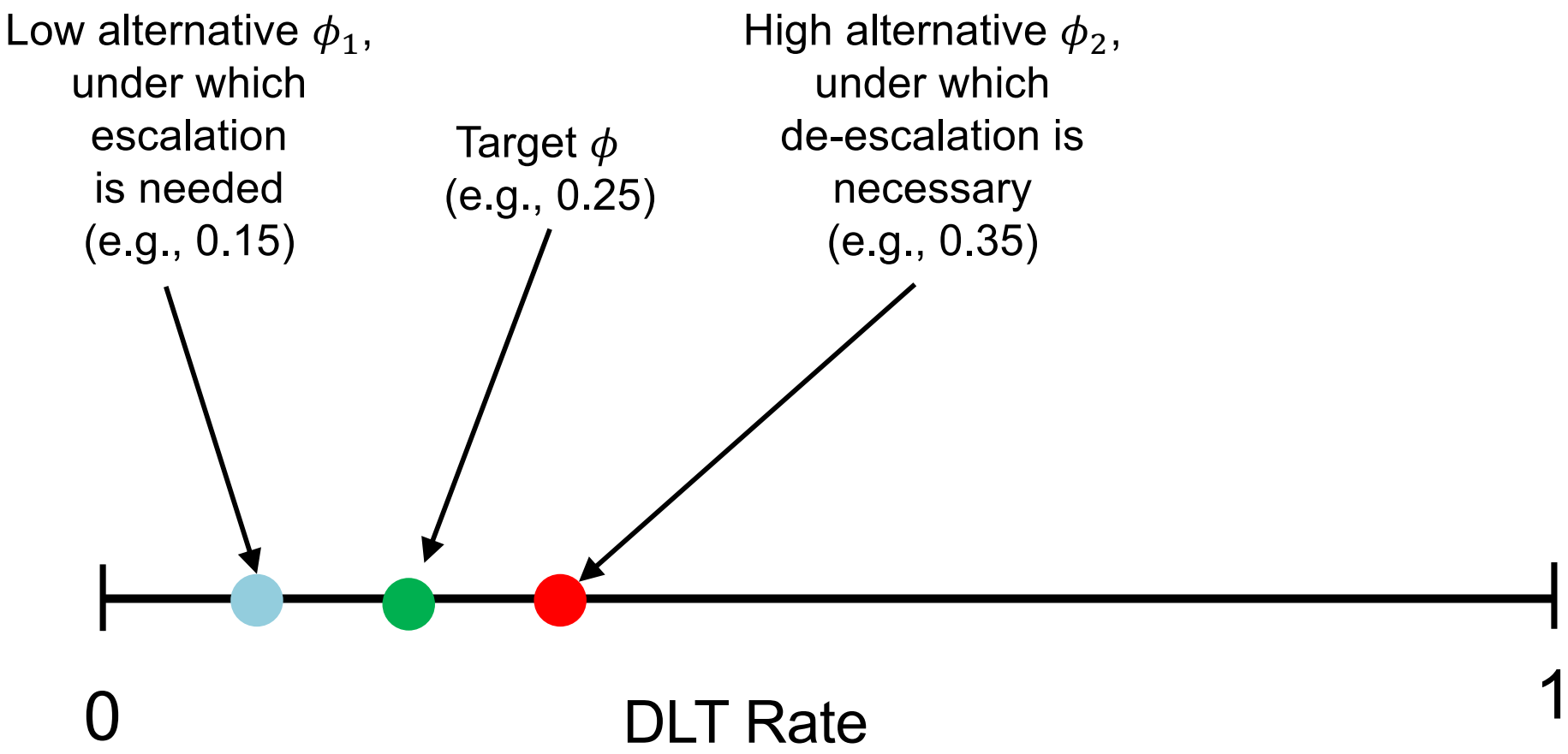
1. The first cohort are treated at the lowest or prespecified dose level
2. At the current dose level j:
   - If $\hat{p}_j \leq \lambda_{1j}(n_j)$, escalate the dose
   - If $\hat{p}_j \geq \lambda_{2j}(n_j)$, deescalate the dose
   - otherwise, retain the current dose

   where $\lambda_{1j}(n_j)$ and $\lambda_{2j}(n_j)$ are arbitrary functions of j and n_j
3. Repeat step 2 until the maximum sample size is reached

- Because $\lambda_{1j}(n_j)$ and $\lambda_{2j}(n_j)$ can freely vary across j and n_j, this class of designs include **ALL possible nonparametric designs** that do not impose a dose-toxicity curve.

Target and Alternatives

H_1: $p_j = \phi_1$; H_0: $p_j = \phi$; H_2: $p_j = \phi_2$



Decision Error Rate

- The probability of making an incorrect decision (i.e., decision error rate) at each of the dose assignments is given by

$$\alpha \equiv \Pr(incorrect\ decision\ on\ dosing)$$

$$= \Pr(H_0)\Pr(E\ or\ D|H_0) + \Pr(H_1)\Pr(D\ or\ S|H_1) + \Pr(H_2)\Pr(S\ or\ E|H_2)$$

$$= \Pr(H_0)\left\{Bin\left(n_j\lambda_{1j}; n_j, \phi\right) + 1 - Bin\left(n_j\lambda_{2j} - 1; n_j, \phi\right)\right\}$$

$$+ \Pr(H_1)\left\{1 - Bin\left(n_j\lambda_{1j}; n_j, \phi_1\right)\right\}$$

$$+ \Pr(H_2)\,Bin(n_j\lambda_{2j} - 1; n_j, \phi_2)$$

Where E is escalation, D is de-escalation, and S is stay.

Optimal Escalation/De-escalation Boundaries

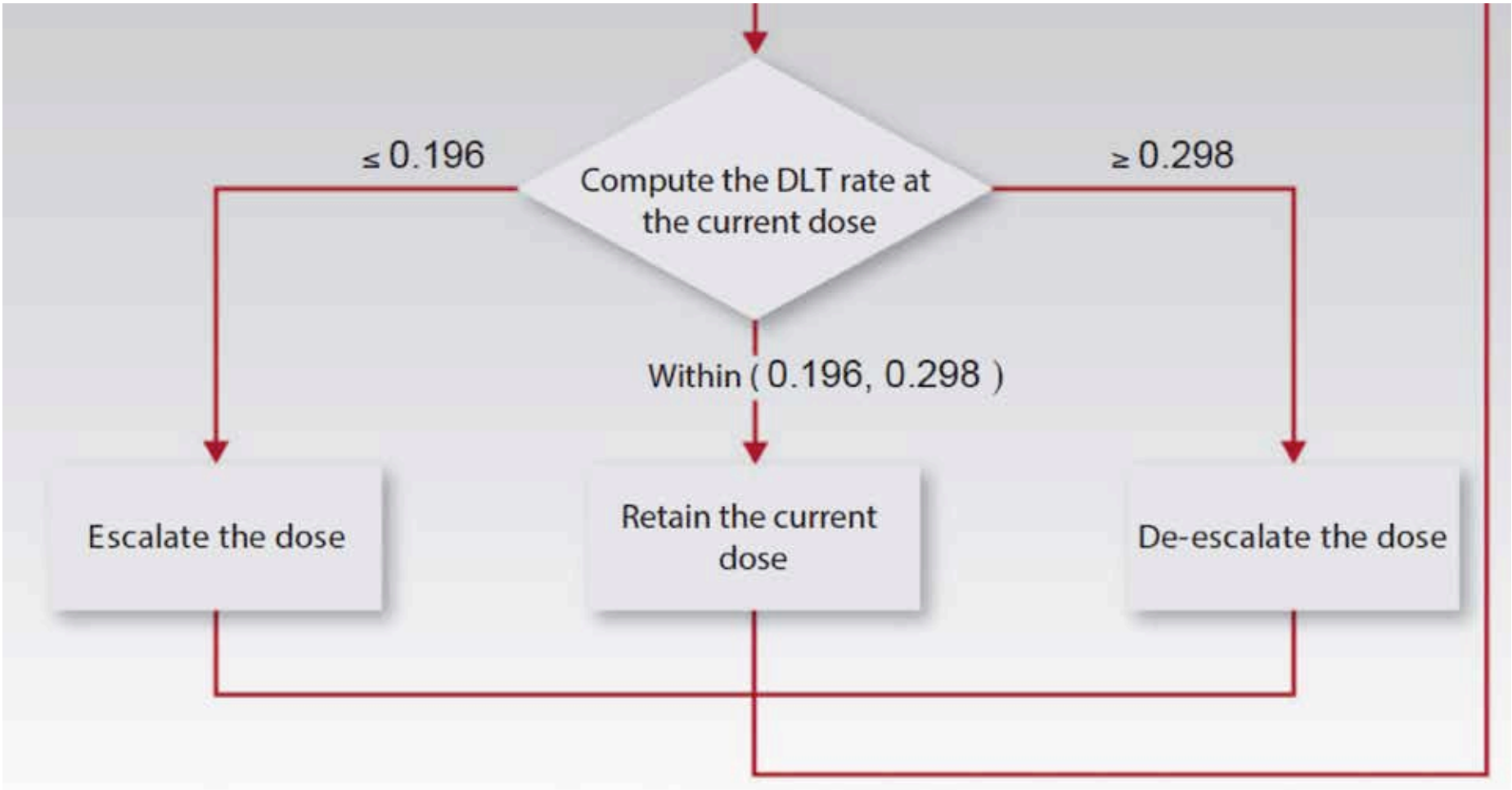
- The dose escalation and de-escalation boundaries (λ_e, λ_d) that minimize the decision error are given by

$$\lambda_e \equiv \lambda_{1j} = \log\left(\frac{1-\phi_1}{1-\phi}\right) \Big/ \log\left(\frac{\phi(1-\phi_1)}{\phi_1(1-\phi)}\right)$$

$$\lambda_d \equiv \lambda_{2j} = \log\left(\frac{1-\phi}{1-\phi_2}\right) \Big/ \log\left(\frac{\phi_2(1-\phi)}{\phi\,(1-\phi_2)}\right)$$

- The optimal escalation/de-escalation boundaries are independent of n_j and j !!
- This makes BOIN extremely simple because the same pair of escalation/de-escalation boundaries can be used throughout of the trial.

BOIN for Target = 25%



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

Remarks on Hypotheses

- The purpose of specifying three hypotheses, H_0, H_1 and H_2, is not to represent the truth and conduct hypothesis testing.
- H_1 and H_2, or more precisely $\delta_1 = \phi_1 - \phi$ and $\delta_2 = \phi_2 - \phi$ represent the minimal differences (or effect sizes) of practical interest to be distinguished from the target DLT rate ϕ (or H_0), under which we want to minimize the average decision error rate for the trial conduct.
- This is analogous to power calculation.

Remarks on Hypotheses

- In practice, we should avoid setting ϕ_1 and ϕ_2 at values very close to ϕ because of the limited power due to small sample sizes of phase I trials.
  - At the significance level of 0.05, we have only 3% power to distinguish 0.35 from 0.25 with 30 patients.
- We highly recommend using the default values $\phi_1 = 0.6\phi$ and $\phi_2 = 1.4\phi$.
  - e.g., when $\phi = 0.25$, $\phi_1 = 0.15$ and $\phi_2 = 0.35$.

Practical Advantages

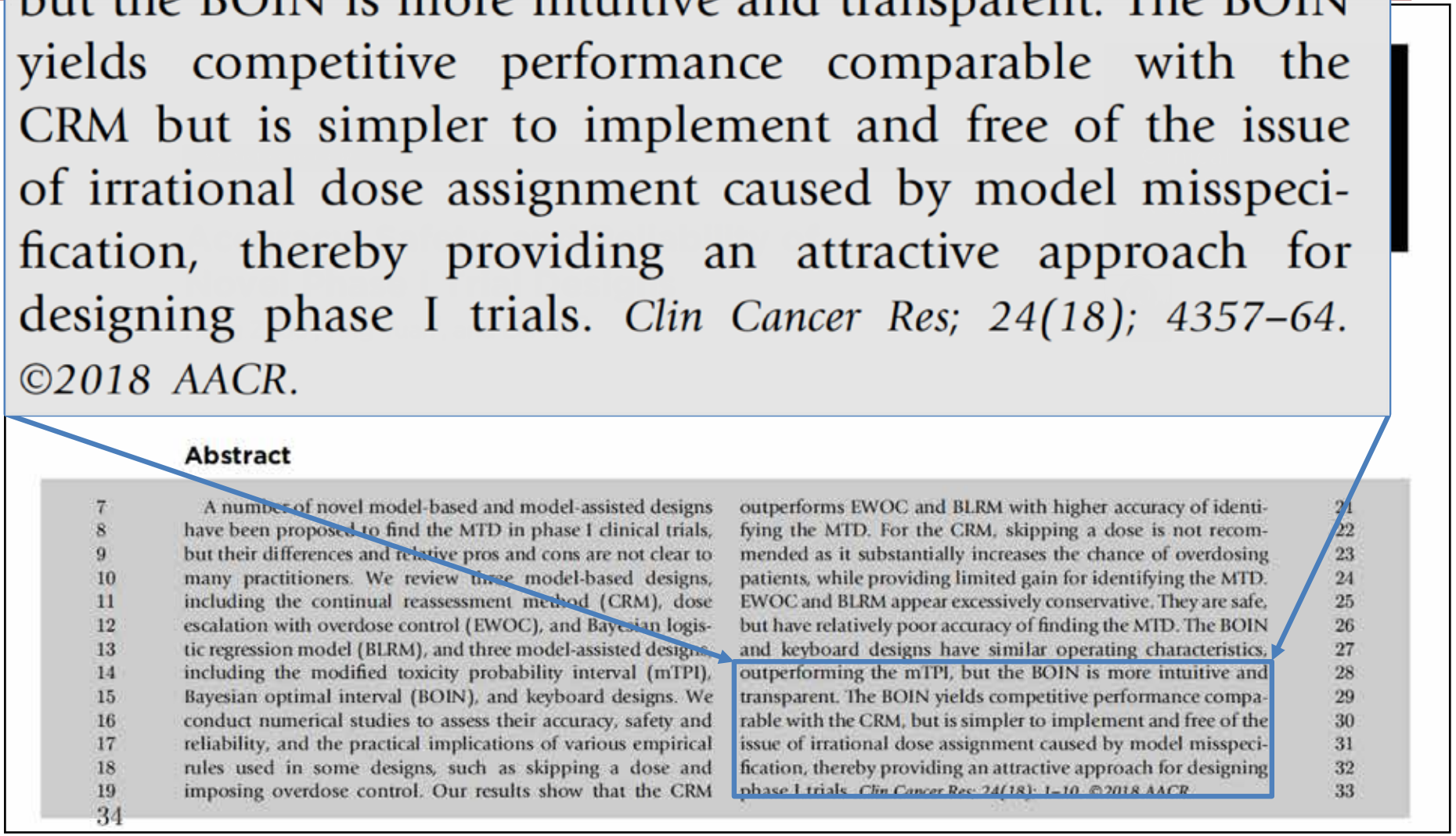
- It is very easy for clinicians and regulatory agents to assess the safety of the trial because BOIN guarantees deescalating the dose when the observed DLT rate $\hat{p}_j$ is higher than the de-escalation boundary λ_d.
  - For example, given a target DLT rate $\phi = 0.25$, we know *a priori* that the BOIN guarantees deescalating the dose if the observed toxicity rate is higher than 0.298.

Practical Advantages

- BOIN design also allows users to easily calibrate the design to satisfy a specific safety requirement mandated by regulatory agents through choosing an appropriate target ϕ.
  - Supposing for a phase I trial with a new compound, the regulatory agent mandates that if the observed DLT rate is higher than 0.25, the dose must be de-escalated.
  - We can easily fulfill that requirement by setting the target DLT rate $\phi = 0.21$, under which the BOIN automatically guarantees de-escalating the dose if the observed DLT rate $\hat{p}_j > \lambda_d = 0.25$.

Performance of BOIN

but the BOIN is more intuitive and transparent. The BOIN yields competitive performance comparable with the CRM but is simpler to implement and free of the issue of irrational dose assignment caused by model misspecification, thereby providing an attractive approach for designing phase I trials. *Clin Cancer Res; 24(18); 4357–64.* ©*2018 AACR.*



Abstract

A number of novel model-based and model-assisted designs have been proposed to find the MTD in phase I clinical trials, but their differences and relative pros and cons are not clear to many practitioners. We review three model-based designs, including the continual reassessment method (CRM), dose escalation with overdose control (EWOC), and Bayesian logistic regression model (BLRM), and three model-assisted designs, including the modified toxicity probability interval (mTPI), Bayesian optimal interval (BOIN), and keyboard designs. We conduct numerical studies to assess their accuracy, safety and reliability, and the practical implications of various empirical rules used in some designs, such as skipping a dose and imposing overdose control. Our results show that the CRM outperforms EWOC and BLRM with higher accuracy of identifying the MTD. For the CRM, skipping a dose is not recommended as it substantially increases the chance of overdosing patients, while providing limited gain for identifying the MTD. EWOC and BLRM appear excessively conservative. They are safe, but have relatively poor accuracy of finding the MTD. The BOIN and keyboard designs have similar operating characteristics, outperforming the mTPI, but the BOIN is more intuitive and transparent. The BOIN yields competitive performance comparable with the CRM, but is simpler to implement and free of the issue of irrational dose assignment caused by model misspecification, thereby providing an attractive approach for designing phase I trials. *Clin Cancer Res; 24(18); 1–10.* ©*2018 AACR.*

Zhou H, Yuan Y and Nie L (2018) *Clinical Cancer Research*, 24(18):4357-4364

Performance of BOIN

DOI: 10.1002/sim.7674

RESEARCH ARTICLE

WILEY Statistics in Medicine

Comparative review of novel model-assisted designs for phase I clinical trials

Heng Zhou[1] | Thomas A. Murray[2] | Haitao Pan[3] | Ying Yuan[1]

[1]Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

[2]Department of Biostatistics, The University of Minnesota, Minneapolis, MN, USA

[3]Department of Biostatistics, St. Jude Children's Research Hospital, Memphis, TN, USA

Correspondence
Ying Yuan, Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA.
Email: yyuan@mdanderson.org

A number of novel phase I trial designs have been proposed that aim to combine the simplicity of algorithm-based designs with the superior performance of model-based designs, including the modified toxicity probability interval, Bayesian optimal interval, and Keyboard designs. In this article, we review these "model-assisted" designs, contrast their statistical foundations and pros and cons, and compare their operating characteristics with the continual reassessment method. To provide unbiased and reliable results, our comparison is based on 10 000 dose-toxicity scenarios randomly generated using the pseudo-uniform algorithm recently proposed in the literature. The results showed that the continual reassessment method, Bayesian optimal interval, and Keyboard designs provide comparable, superior operating characteristics, and each outperforms the modified toxicity probability interval design. These designs are more likely to correctly select the maximum tolerated dose and less likely to overdose patients.

Zhou H, et al. (2018) *Statistics in Medicine*, 37, 2208-2222.

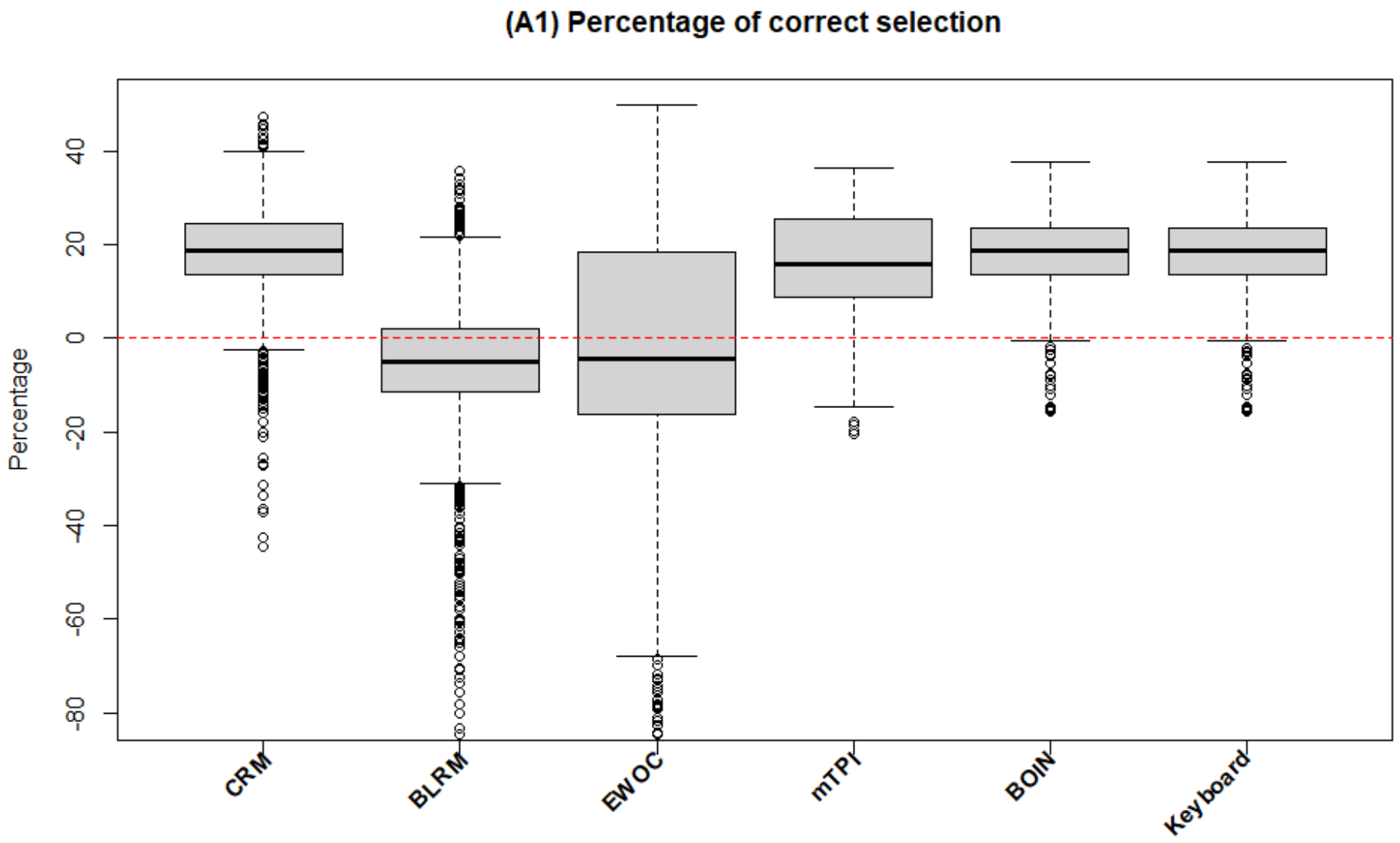
Numerical Study

- Target $\phi = 0.25$; $J = 6$ dose levels; maximum sample size = 36; cohort size= 1 or 3
- 1000 random scenarios generated using pseudo-uniform algorithm (Clertant and O'Quigley, 2017).
- 2000 simulated trials for each scenario.
- Compared 3 model-based designs (i.e., CRM, EWOC and BLRM) and 3 model-assisted designs (i.e., mTPI, keyboard and BOIN).

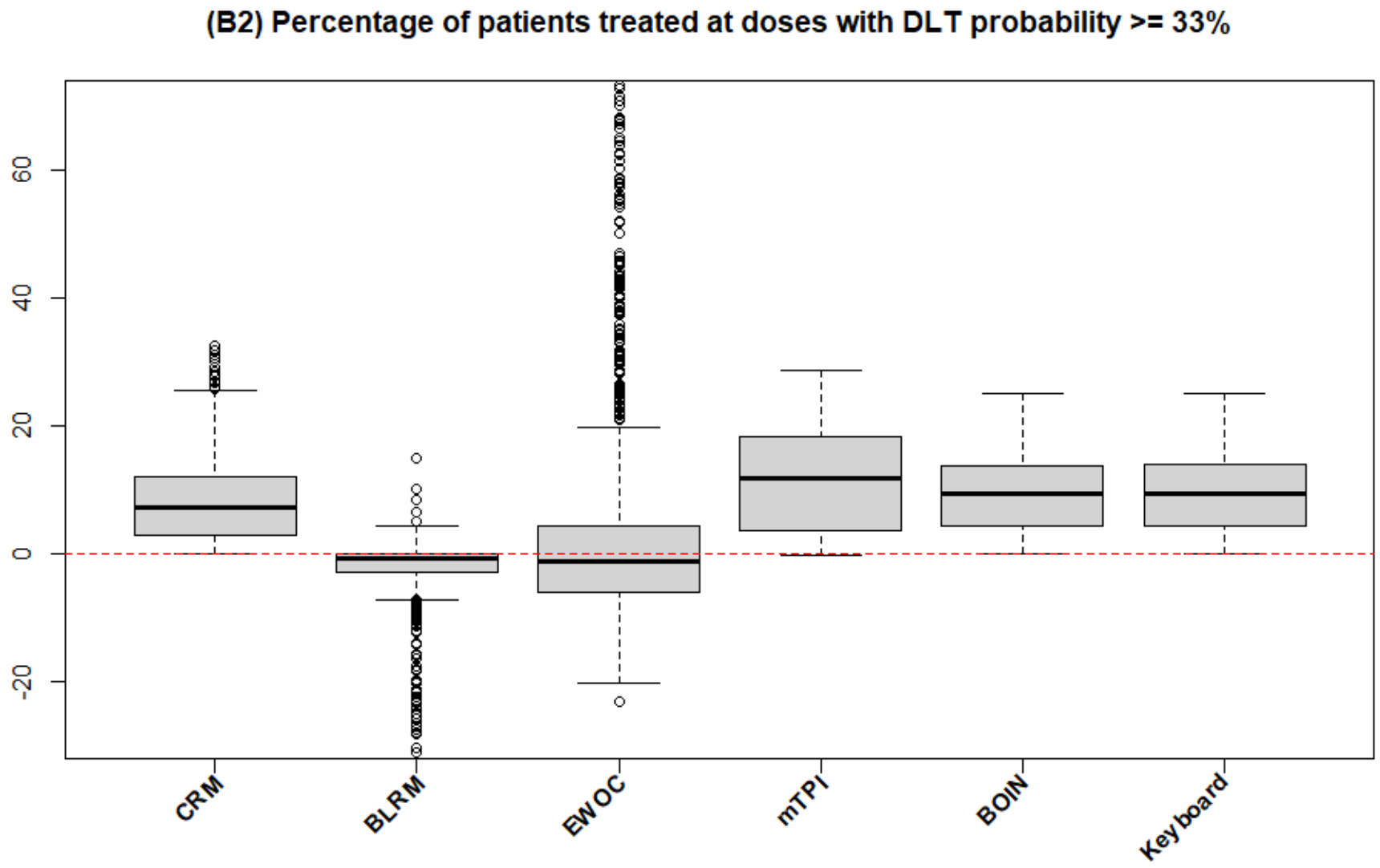
Numerical Study

- 3+3 design is used as the reference to present the performance of novel designs
- For example, PCS of CRM will be presented as “PCS of CRM – PCS of 3+3 design”, therefore 0 means equal performance, positive value means better performance.
- For example, the risk of overdosing of CRM will be presented as “the risk of overdosing of CRM – the risk of overdosing of 3+3 design”, therefore 0 means equal performance, negative value means better performance.

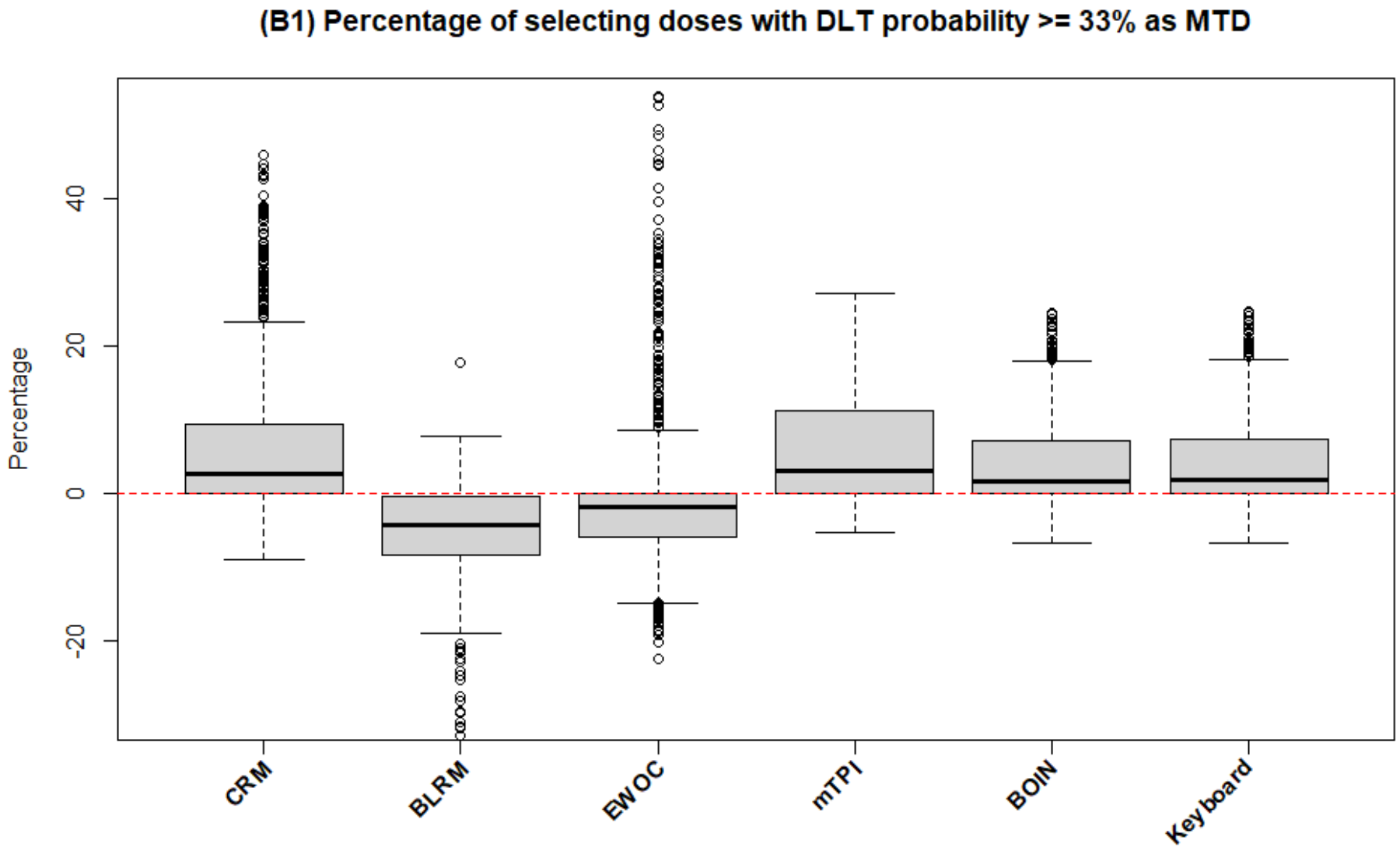
Percentage of correct selection



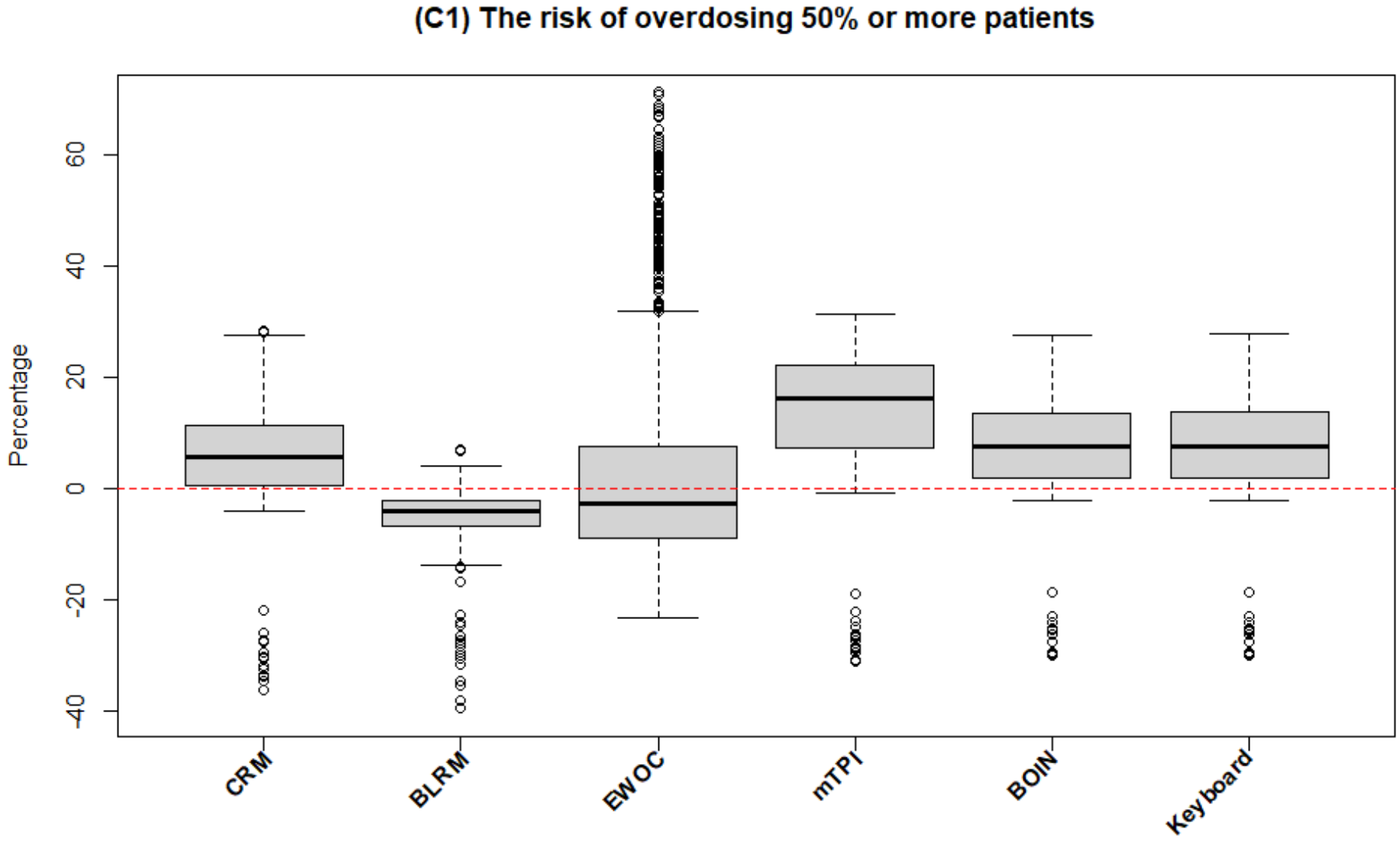
% of patients treated at dose with DLT rate >= 33%



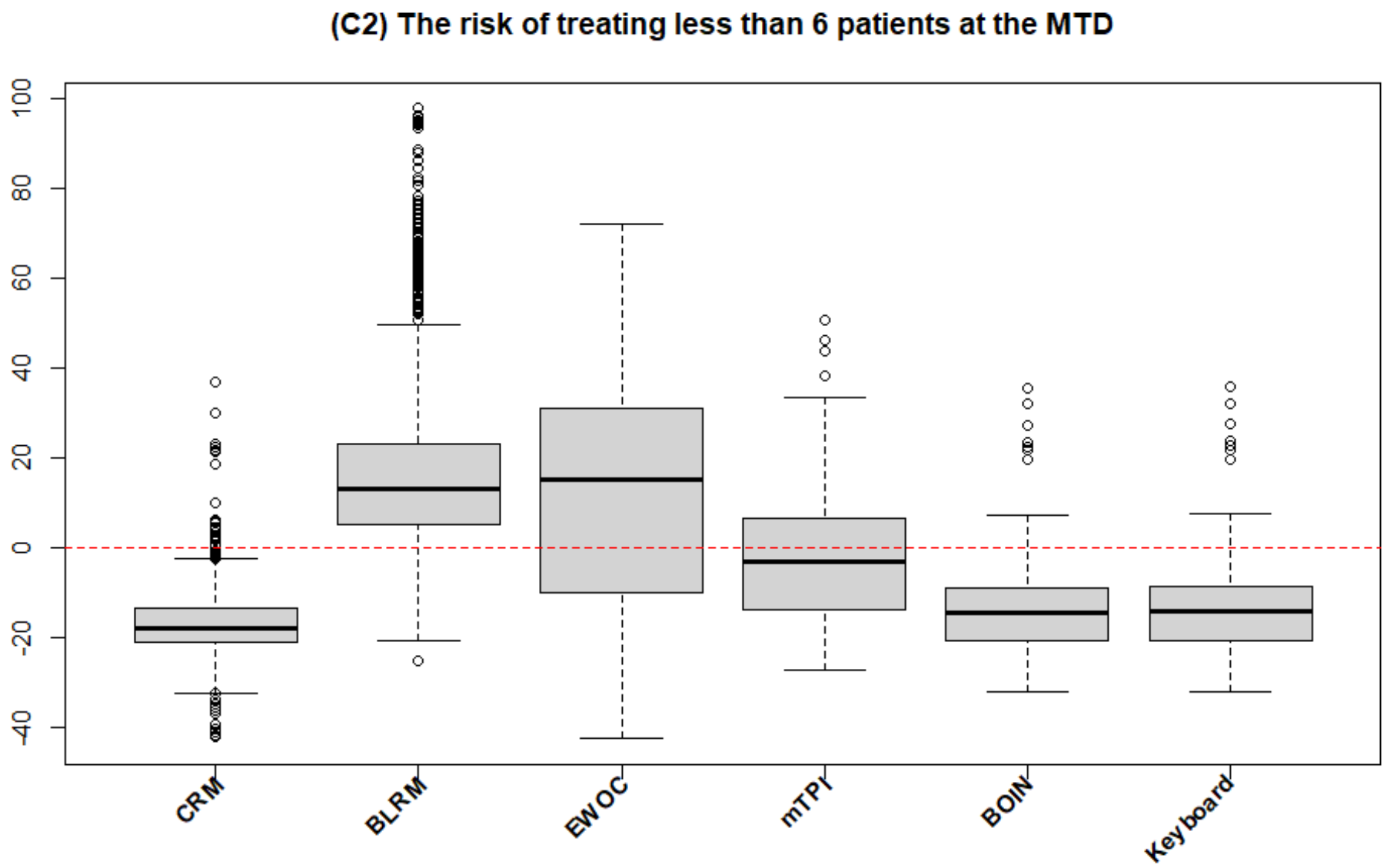
% of selecting doses with DLT rate >= 33%



% of trials overdosing >50% patients

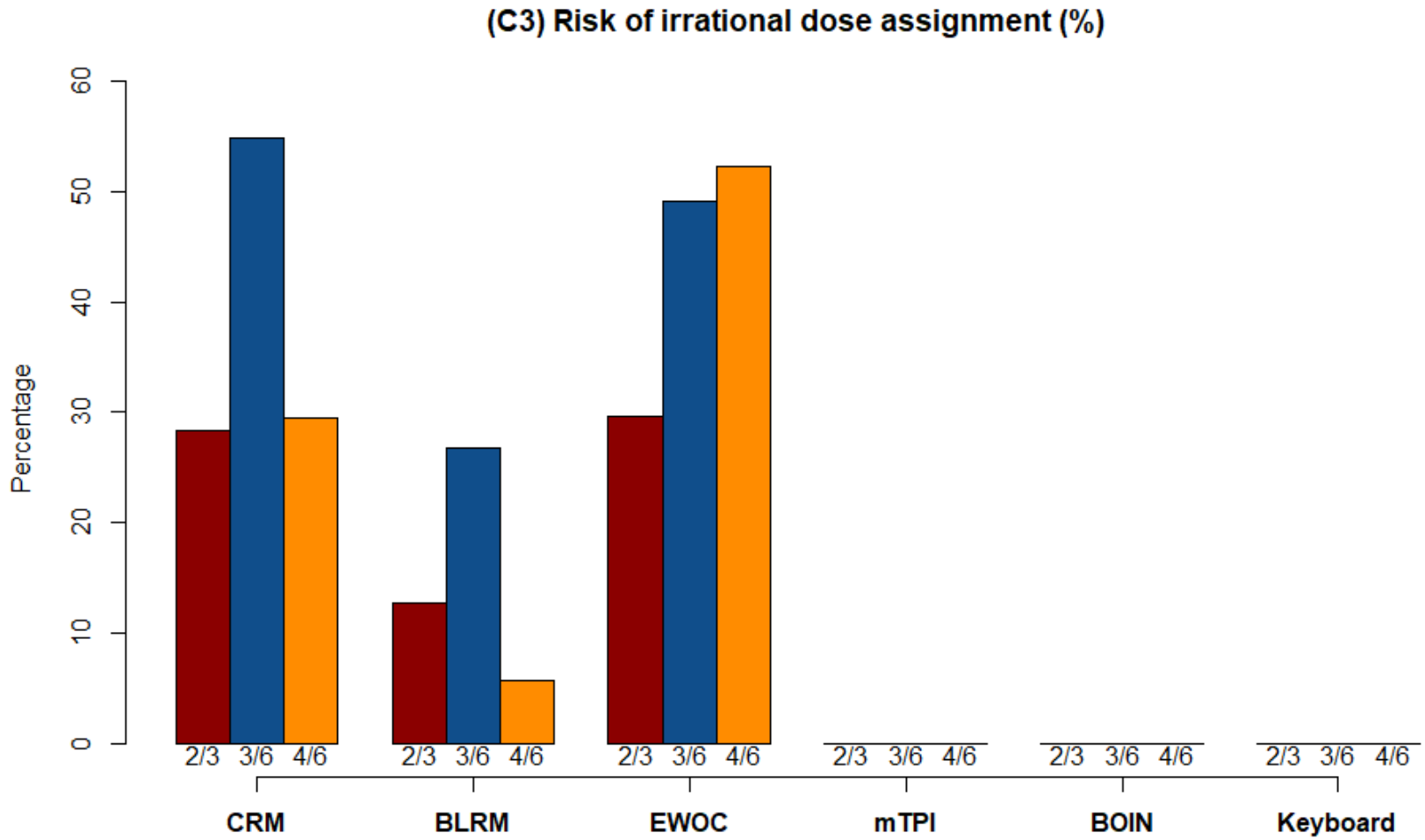


% of trials treating < 6 patients at MTD



Irrational dose assignment

- Percentage of time failing to de-escalate when 2/3 or ≥3/6 have DLT



Summary

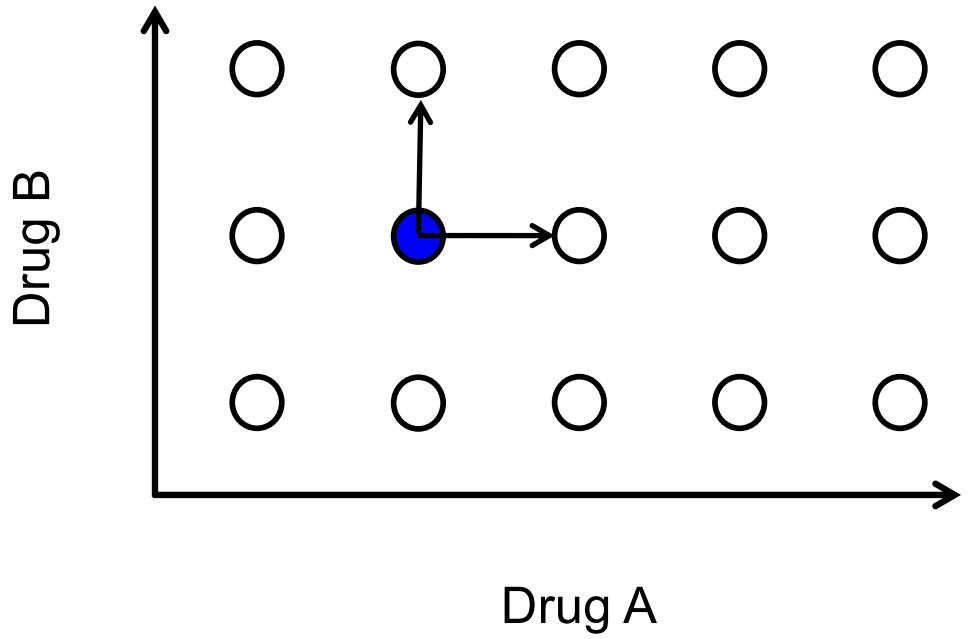
- BOIN yields similar performance as the CRM, but is more transparent and easier to implement.
- BOIN does not assume a parametric model on the dose-toxicity curve, thus is free from the issue of making irrational dose assignment during the trial conduct.
- BOIN is more accurate, safer, and also simpler than mTPI.

BOIN Drug-Combination Design

- Lin and Yin (2017) extended the BOIN to drug-combination trials.
- BOIN drug-combination design uses the same rule to determine dose escalation and de-escalation.
- The difference is that when we decide to escalate/de-escalate the dose, there are more than one neighbor doses to which we can move to, i.e., we can change the dose of drug A or the dose of drug B.

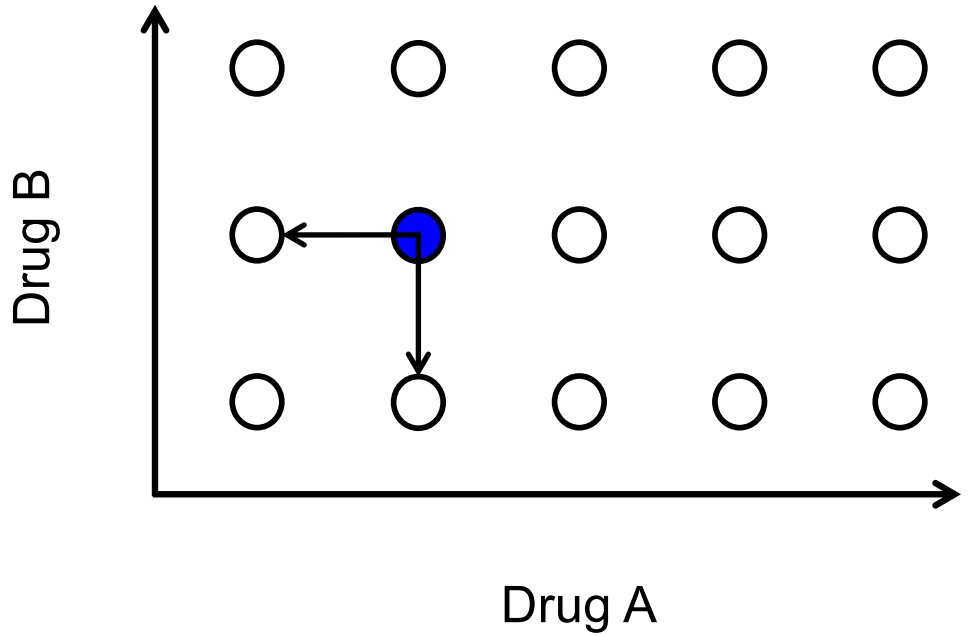
Dose Escalation Rule

- When $\hat{p} < \lambda_e$, we escalate the dose to the neighbor dose that has a higher posterior probability located in (λ_e, λ_d).



Dose De-escalation Rule

- When $\hat{p} > \lambda_d$, we de-escalate the dose to the neighbor dose that has a higher posterior probability located in (λ_e, λ_d).



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).
- The late-onset toxicity is also common in conventional radiochemotherapy

Logistic Difficulty with Late-onset Toxicity

- Late-onset toxicity causes 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, five new patients will be accrued while waiting to evaluate the previous three patients' outcomes.
- The question is: how can new patients receive timely treatment when the previous patients' outcomes are pending?

Logistic Difficulty with Fast Accrual

- The same logistic difficult occurs 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, five new patients will accrue while waiting to evaluate the previous three patients' outcomes.
- We must determine how to provide them with timely treatment.

Existing Methods for Late-onset Toxicity

- Several designs have been developed to accommodate late-onset toxicity.
- Algorithm-based approach
  - Rolling 6 design (Skolnik et al., 2008)
- Model-based approach
  - Time-to-event CRM (TITE-CRM; Cheung and Chappell, 2000)
  - Data argumentation CRM (DA-CRM; Liu, Yuan and Yin, 2013)

Rolling 6 Design

- A modification of the 3+3 design
- Pros: transparent and easy to implement
- Cons: inherits the drawbacks of the 3+3 design
  - Cannot target a specific DLT rate
  - Low accuracy to identify the MTD
  - Treat an excessive number of patients at low subtherapeutic doses

Table 1. Comparison of Decision Properties for the 3 + 3 *v* Rolling Six Design

	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		
4	0	0, 1, 2	4, 3, 2	—	n	—	n
4	0	3	1	—	n	n	n
4	0	4	0	—	n + 1	n	n
4	1	0, 1	3, 2	—	n	—	n
4	1	2	1	n	n	—	n
4	1	3	1	n	n	n	n
4	≥ 2	Any	Any	n − 1	n − 1	n − 1	n − 1
5	0	0, 1, 2	5, 4, 3	–	n	–	n
5	0	3, 4	2, 1	–	n	n	n
5	0	5	0	–	n + 1	n	n
5	1	0, 1	4, 3	–	n	–	n
5	1	2	2	n	n	–	n
5	1	3, 4	1, 0	n	n	n	n
5	≥ 2	Any	Any	n − 1	n − 1	n − 1	n − 1
6	0	0, 1, 2	6, 5, 4	—	Suspend	—	Suspend
6	0	3, 4	3, 2	—	Suspend	Suspend	Suspend
6	0	5, 6	1, 0	—	n + 1	MTD	MTD
6	1	0, 1	5, 4	—	Suspend	—	Suspend
6	1	2	3	Suspend	Suspend	—	Suspend
6	1	3, 4	2, 1	Suspend	Suspend	Suspend	Suspend
6	1	5	0	n + 1	n + 1	MTD	MTD
6	≥ 2	Any	Any	n − 1	n − 1	n − 1	n − 1

NOTE. This table does not take into account inevaluable patients.
Abbreviations: DLT, dose-limiting toxicity; MTD, maximum-tolerated dose.
*n is the current dose level of patients enrolled; n + 1 and n −1 represent dose level escalation and de-escalation, respectively.

Follow-up Time of Pending Patients

- Rolling 6 is also grossly inefficient because of Ignoring the follow-up time of pending patients
- Quiz: Assume a 90-day follow-up window and that two pending patients A and B have been followed 3 days and 87 days, respectively, which patient contains more information?
- Follow-up time of a pending patient contains rich information how likely that patient will experience DLT

Model-based Approaches

- TITE-CRM
  - The follow-up time of pending patients contains partial information on their toxicity outcomes
  - Weights pending patients by their follow-up times, resulting in pseudo likelihood
- DA-CRM
  - Treat unobserved toxicity outcomes as missing data
  - Use a Bayesian model to predict the missing data based on the true likelihood
- Both designs outperform the rolling 6 design, but are complicated to implement and subject to the influence of model misspecification

Can we have a design that is as simple as the rolling 6 design, but performs as well as the model-based design (e.g., TITE-CRM)?

YES!

TITE-BOIN

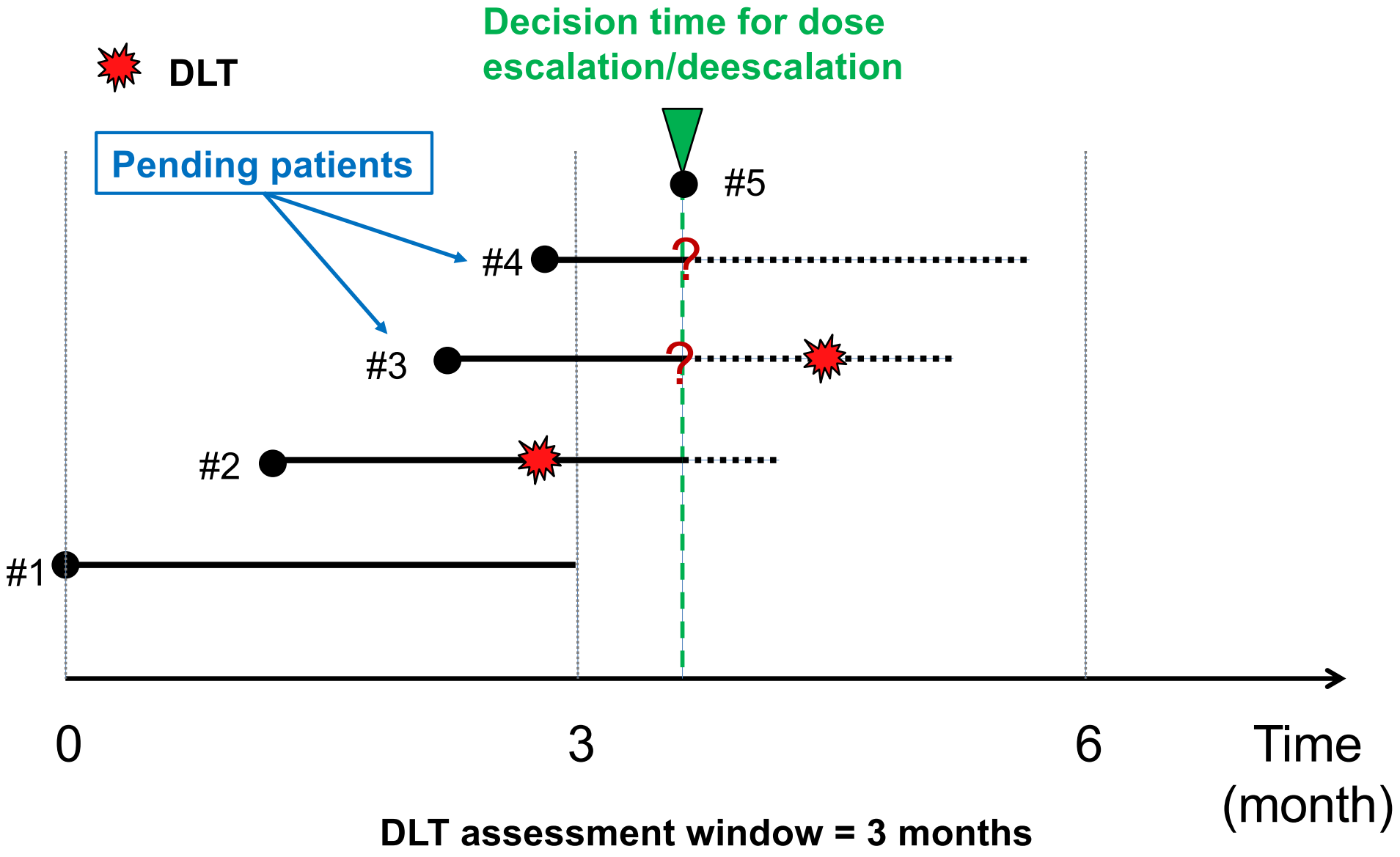
A model-assisted design!

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 n patients are enrolled at the current dose, r patients have completed the DLT assessment (i.e., their DLT data y_i are observed), denoting this set of patients as O.

Notation

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


DLT
Decision time for dose escalation/deescalation
Pending patients
#5
#4
#3
#2
#1
?
?
0
3
6
Time (month)
DLT assessment window = 3 months

BOIN under Late-onset Toxicity

- BOIN makes decision based on the empirical estimate (i.e., MLE) 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

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

$$= \frac{s + \frac{p}{1-p}(c - \mathrm{STFT})}{n}$$

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.

Impute Missing/Pending Data

- This approach is known as single mean imputation (SMI, Little and Rubin; 2012).
- SMI yields an unbiased and consistent point estimate (Little and Rubin; 2012).
- One drawback of SMI is that the resulting variance estimate is biased because of ignoring the imputation uncertainty.
- In our case, this is not a concern as the decision rules of the BOIN only rely on the point estimate of p.

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			No. treated	No. DLTs	No. data pending	STFT		
			Escalate	Stay	De-escalate				Escalate	Stay	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	Stay	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

- In some trial, prior information is available on the distribution of the time to toxicity
  - For example, for a certain drug, we may know *a priori* that the DLT is more likely to occur in the later part of the DLT assessment window $[0.5T, T]$.
- The prior information can be conveniently incorporated into the TITE-BOIN by using weighted STFT (WSTFT)

Weighted STFT (WSTFT)

- 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
- 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!

STFT ⟶ WSTFT

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.

TITE-BOIN vs R6 and TITE-CRM

Design characteristics	R6	TITE-CRM	TITE-BOIN
Can it target any prespecified DLT rate?	No	Yes	Yes
Allows to use a cohort size other than 3?	No	Yes	Yes
Uses follow-up time data from pending patients to make efficient decision of dose escalation and de-escalation?	No	Yes	Yes
Can sample size be calibrated to ensure good operating characteristics?	No	Yes	Yes
Can the number of patients treated at the MTD be more than 6?	No	Yes	Yes
Can dose escalation/de-escalation rule be pre-tabulated for simple implementation?	Yes	No	Yes
Requires complicated, repeated estimation of the dose-toxicity curve model?	No	Yes	No

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

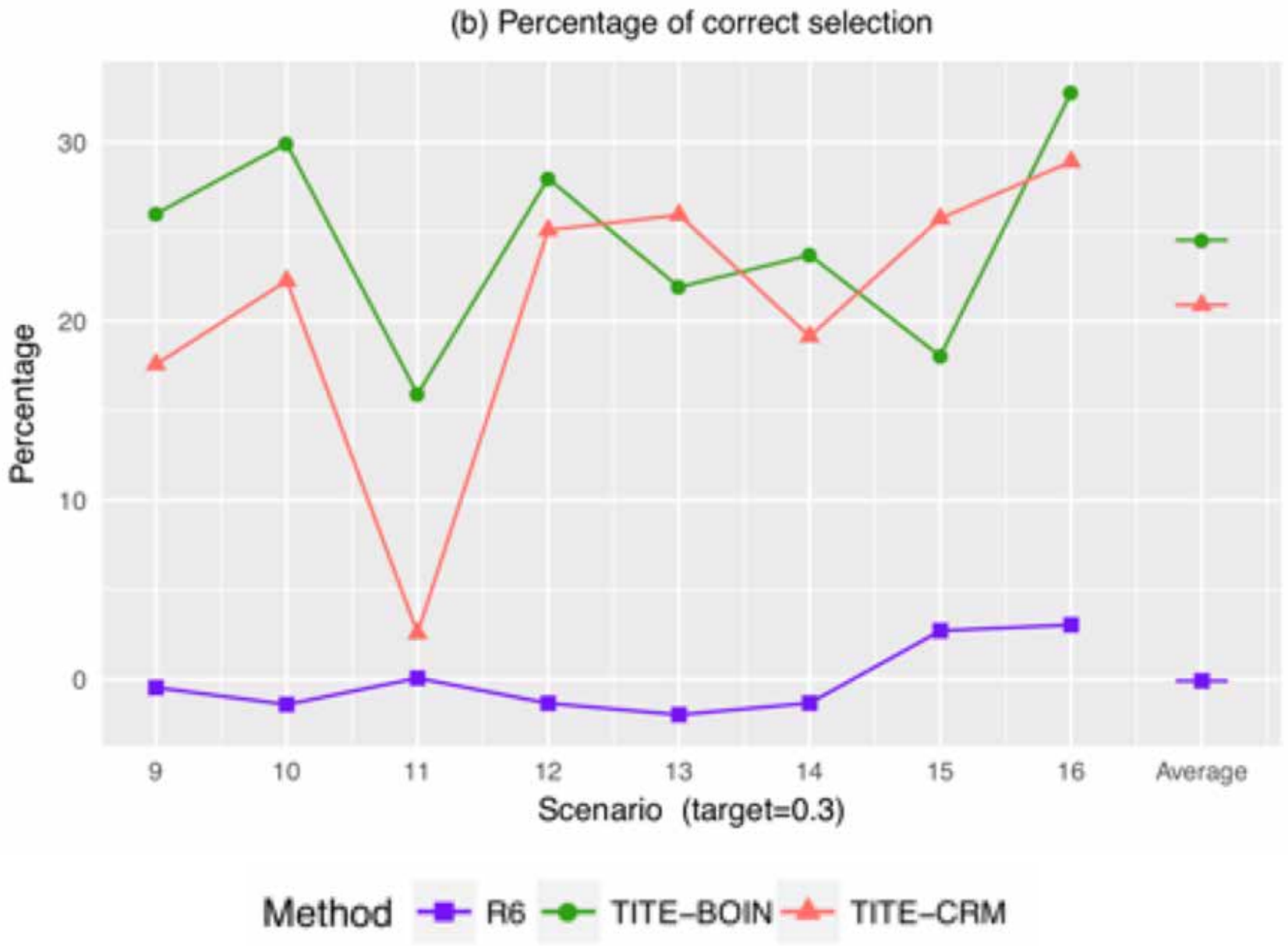
Simulation

- Compared TITE-BOIN, 3+3 design, R6 design, and TITE-CRM.
- 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.
- For the 3+3 design, a new cohort is enrolled only when the previous cohort’s DLT data are cleared.

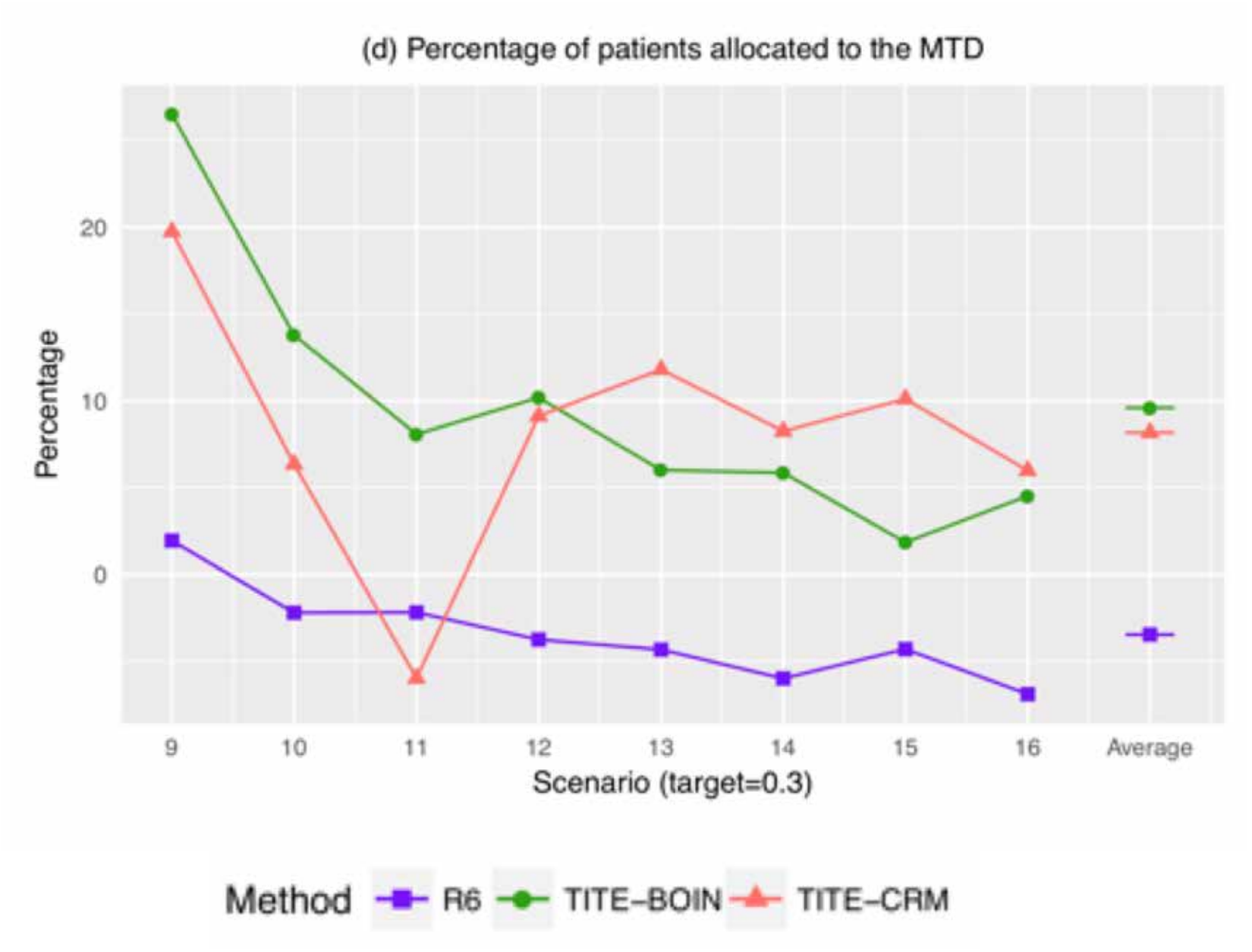
Performance Metrics

- 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)
- Percentage of “regretful” trials that failed to de-escalate the dose when 2 out of the first 3 patients had DLTs at any dose.
- Average trial duration

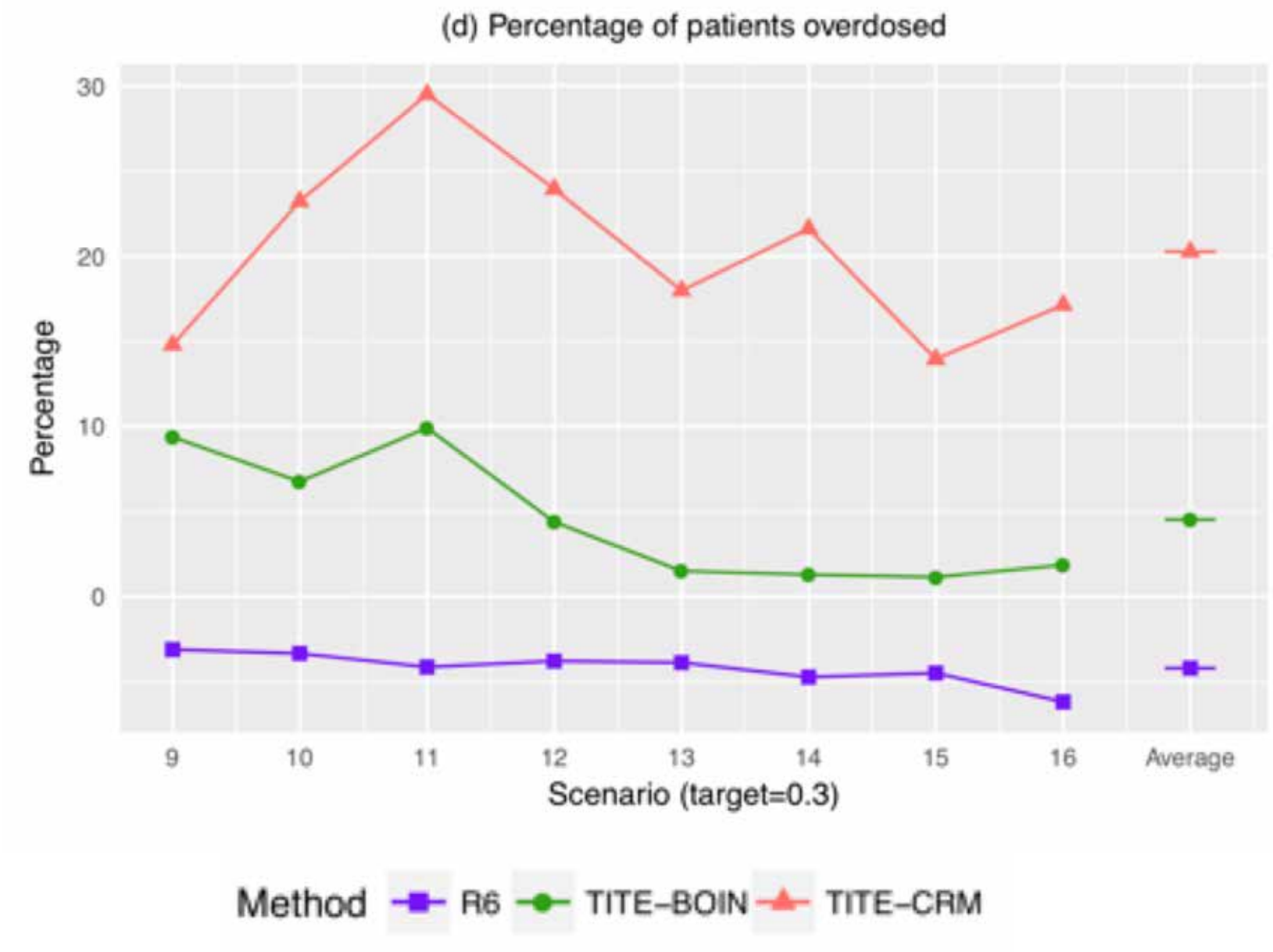
Percentage of correct selection



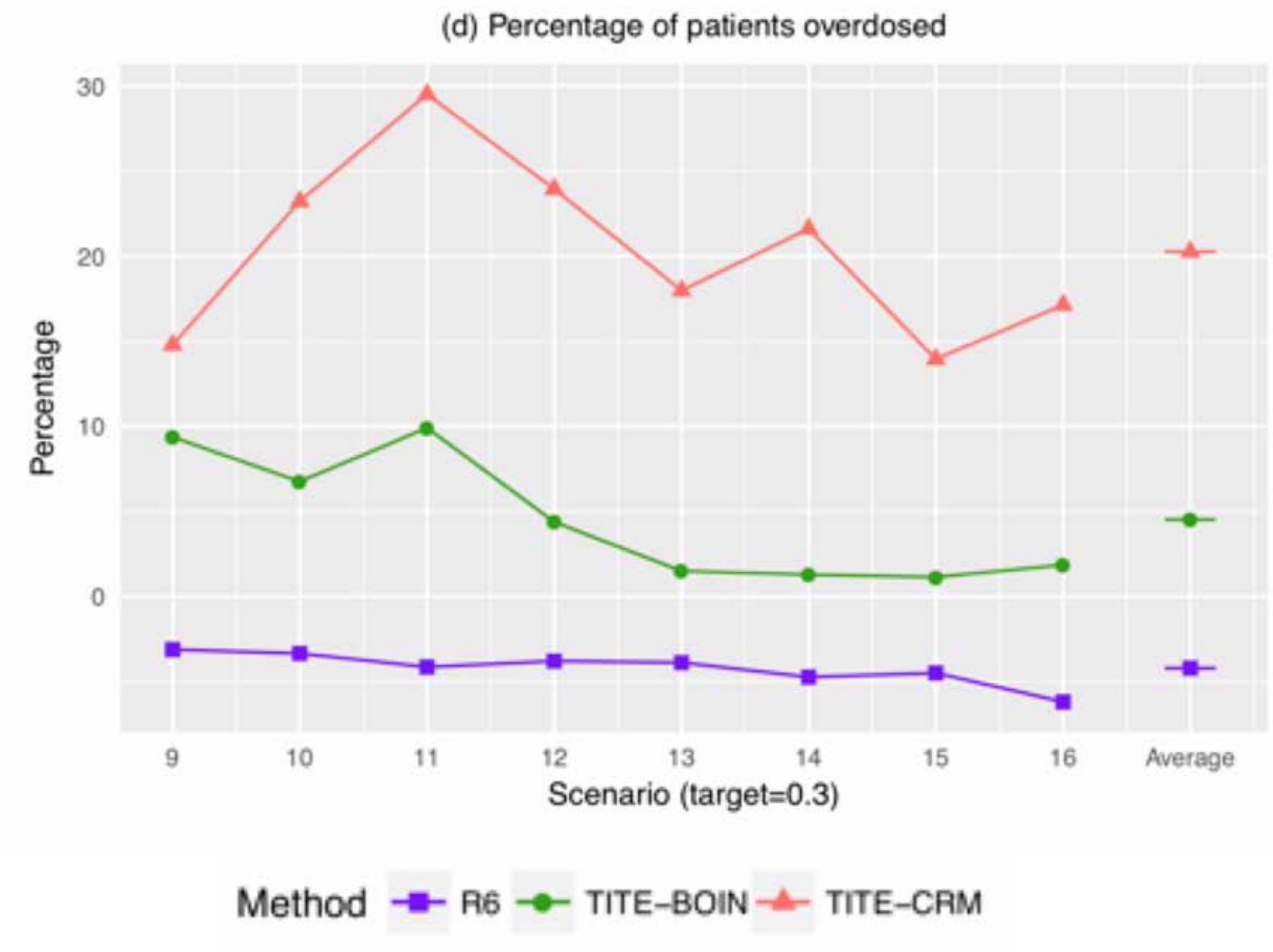
Percentage of patients treated at MTD



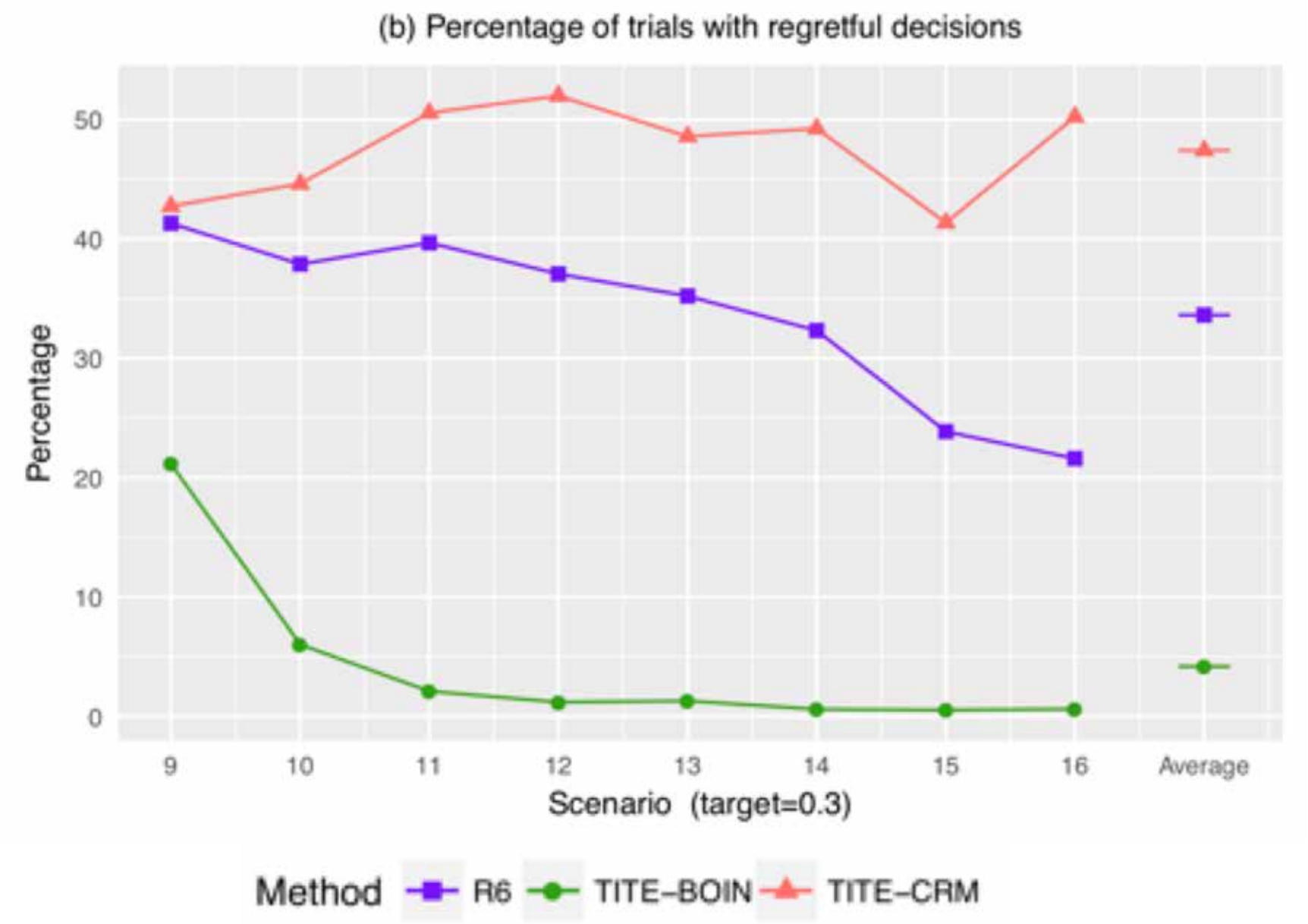
Percentage of patients overdosed



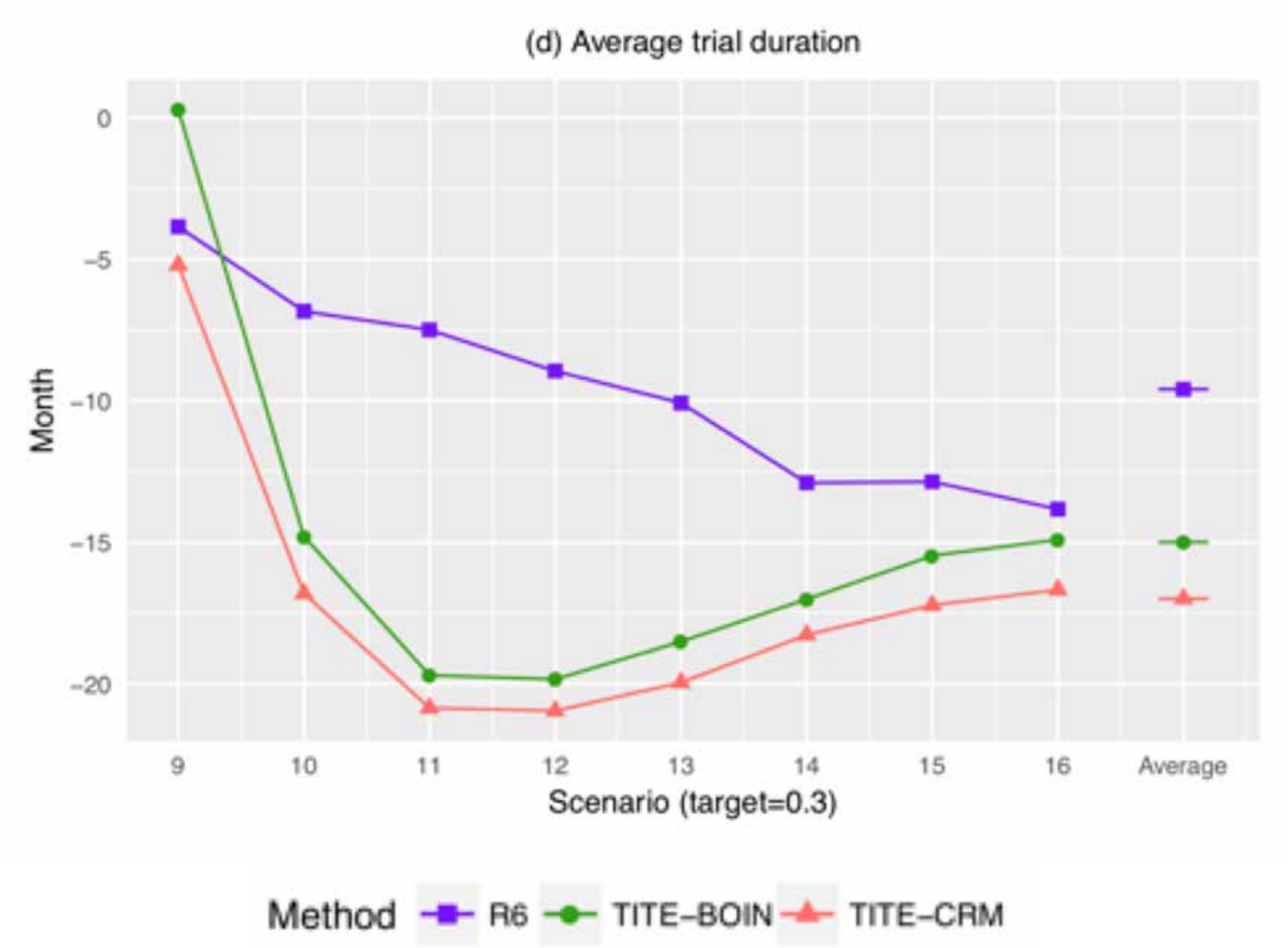
Selection percentage of a dose above MTD



Percentage of “regretful” trials



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.

Statistics in CCR

Clinical Cancer Research

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

Ying Yuan[1], Ruitao Lin[1,2], Daniel Li[3], Lei Nie[4], and Katherine E. Warren[5]

Abstract

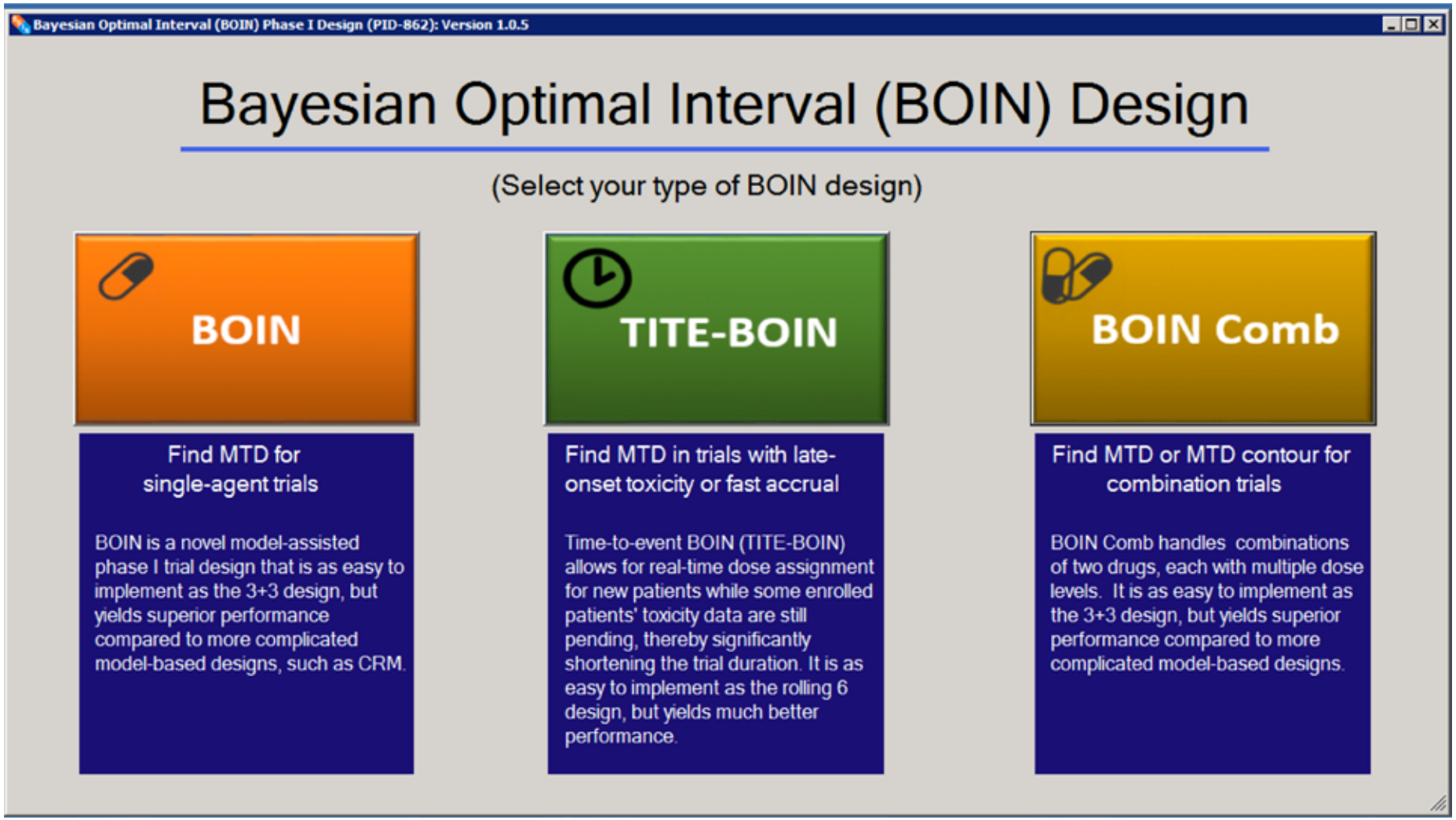
Late-onset toxicity is common for novel molecularly targeted agents and immunotherapy. It causes major logistic difficulty for existing adaptive phase I trial designs, which require the observance of toxicity early enough to apply dose-escalation rules for new patients. The same logistic difficulty arises when the accrual is rapid. We propose the time-to-event Bayesian optimal interval (TITE-BOIN) design to accelerate phase I trials by allowing for real-time dose assignment decisions for new patients, whereas some enrolled patients' toxicity data are still pending. Similar to the rolling six design, the TITE-BOIN dose-escalation/deescalation rule can be tabulated before the trial begins, making it transparent and simple to implement, but is more flexible in choosing the target DLT rate and has higher accuracy to identify the MTD. Compared with the more complicated model-based time-to-event continuous reassessment method (TITE-CRM), the TITE-BOIN has comparable accuracy to identify the MTD, but is simpler to implement with substantially better overdose control. As the TITE-CRM is more aggressive in dose escalation, it is less likely to underdose patients. When there is no pending data, the TITE-BOIN seamlessly reduces to the BOIN design. Numerical studies show that the TITE-BOIN design supports continuous accrual, without sacrificing patient safety nor the accuracy of identifying the MTD, and therefore has great potential to accelerate early phase drug development. *Clin Cancer Res; 24(20); 1–12. ©2018 AACR.*

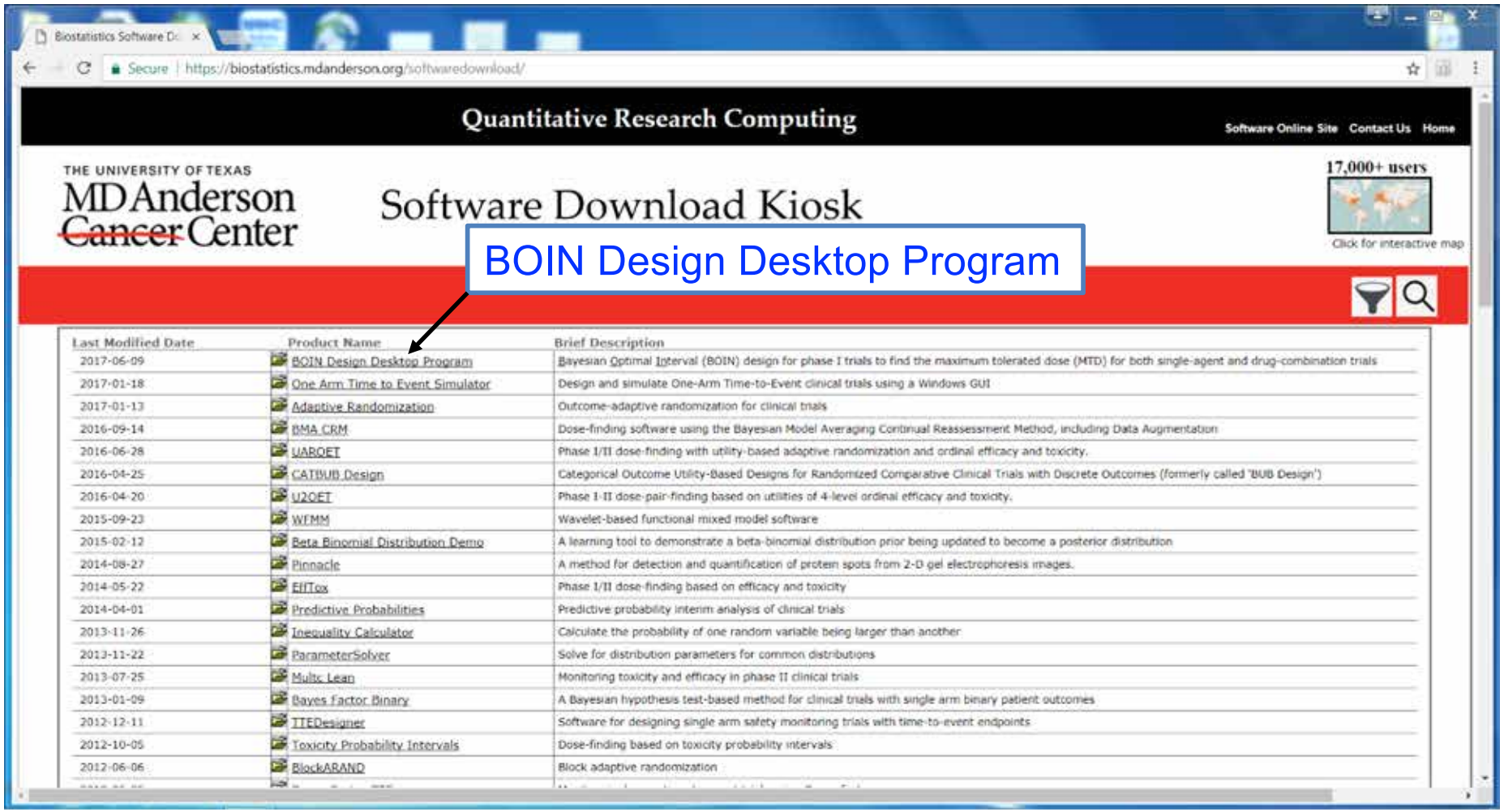
Yuan Y, Lin R, Li D, Nie L and Warren KE (2018) *Clinical Cancer Research*, 24(20):4921-4930.

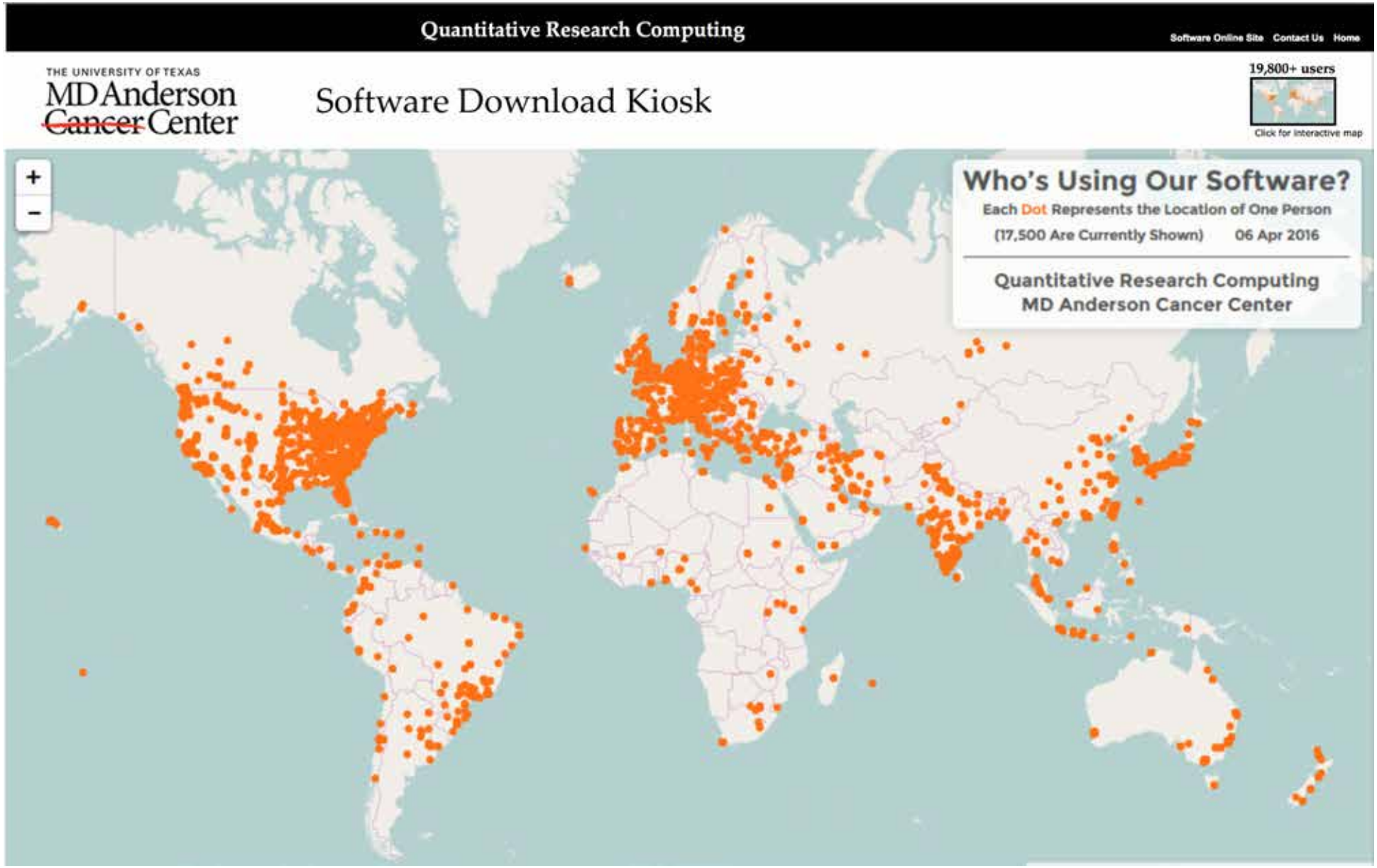
Software

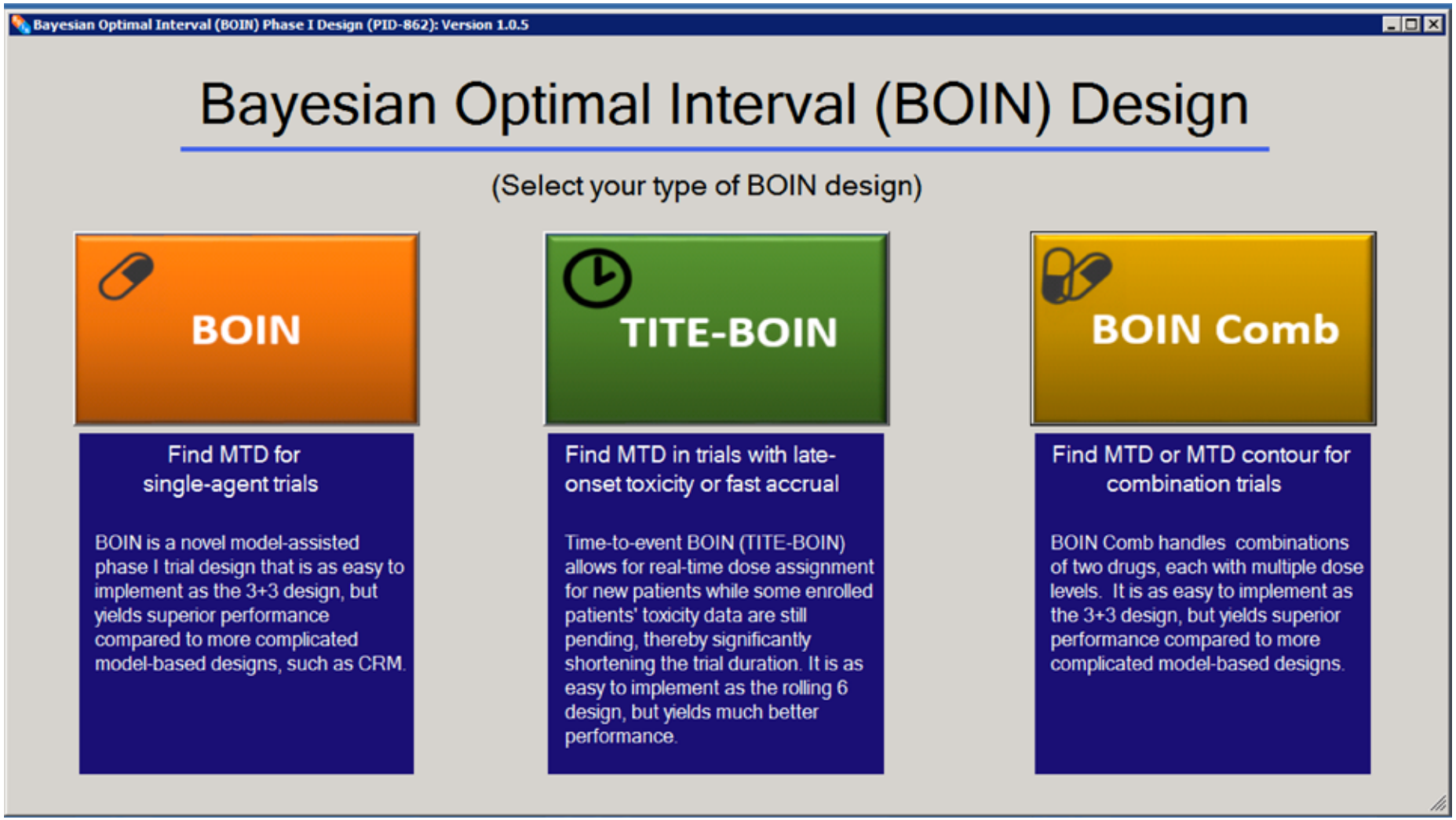
- Windows desktop program for TITE-BOIN is freely available at the MD Anderson Software Download Website https://biostatistics.mdanderson.org/softwaredownload/SingleSoftware.aspx?Software_Id=81.
- Web applications for TITE-BOIN is freely available at http://www.trialdesign.org.

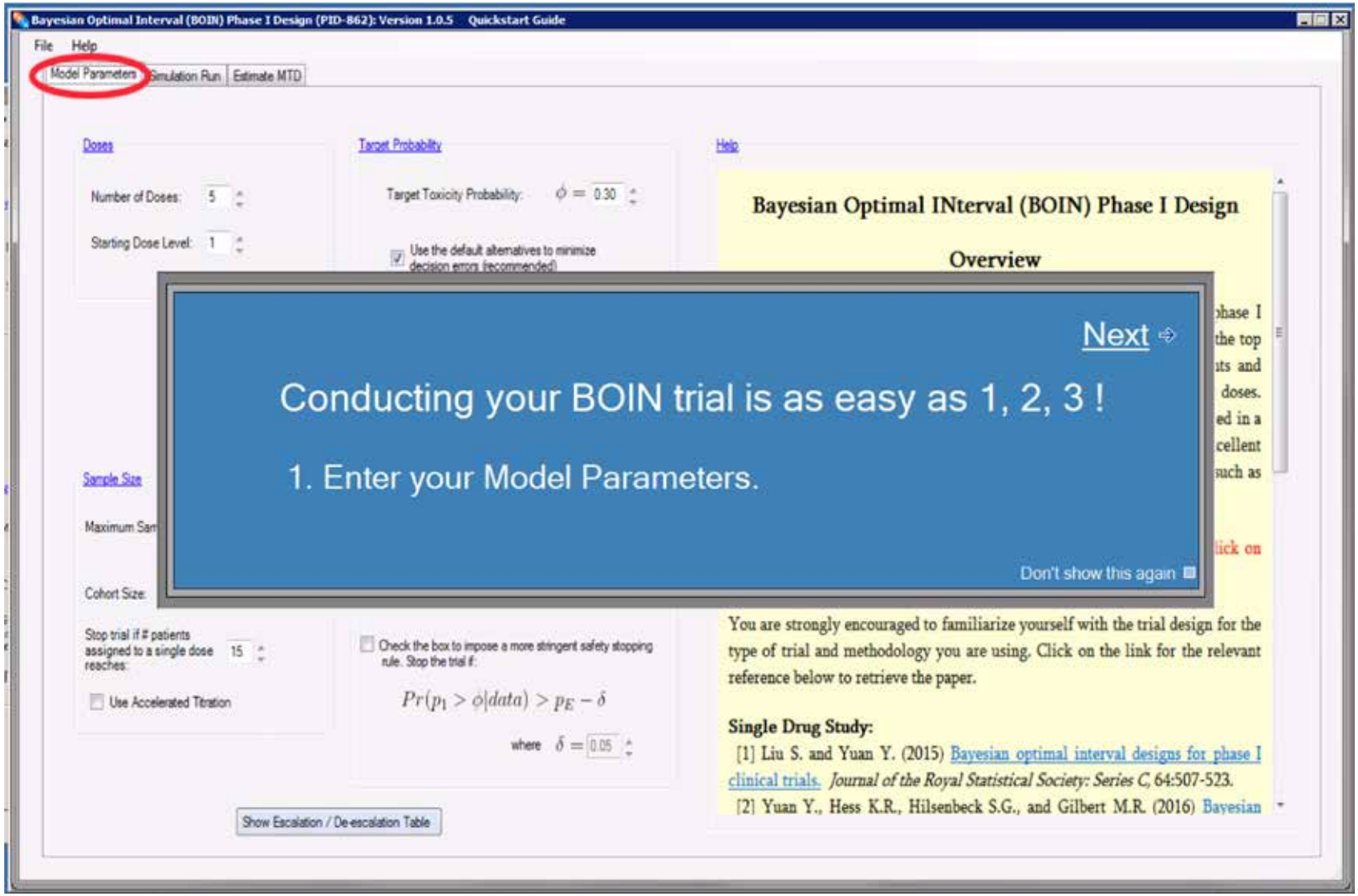
Software

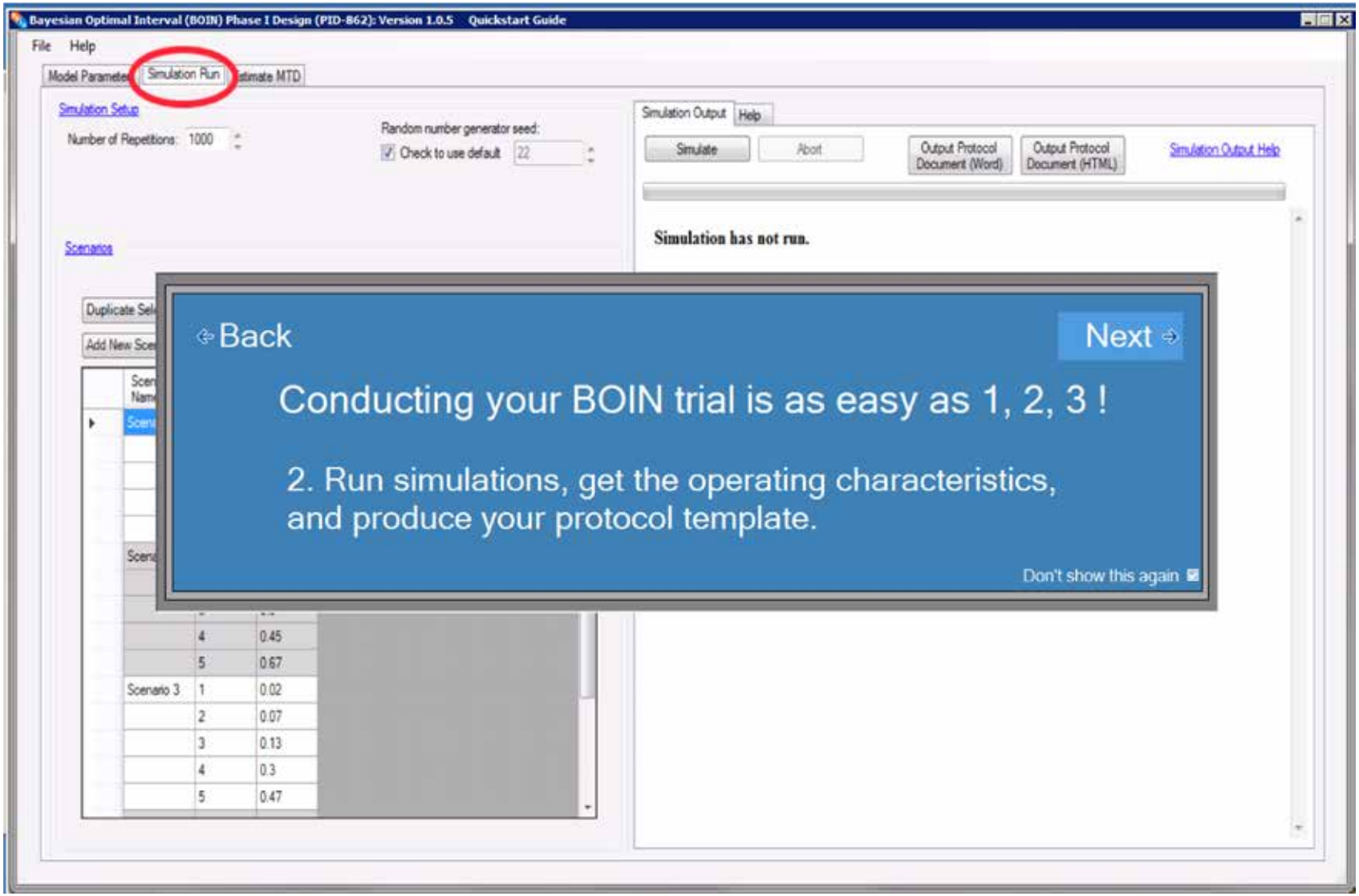

Bayesian Optimal Interval (BOIN) Phase I Design (PID-862): Version 1.0.5
Bayesian Optimal Interval (BOIN) Design
(Select your type of BOIN design)
BOIN
Find MTD for single-agent trials
BOIN is a novel model-assisted phase I trial design that is as easy to implement as the 3+3 design, but yields superior performance compared to more complicated model-based designs, such as CRM.
TITE-BOIN
Find MTD in trials with late-onset toxicity or fast accrual
Time-to-event BOIN (TITE-BOIN) allows for real-time dose assignment for new patients while some enrolled patients' toxicity data are still pending, thereby significantly shortening the trial duration. It is as easy to implement as the rolling 6 design, but yields much better performance.
BOIN Comb
Find MTD or MTD contour for combination trials
BOIN Comb handles combinations of two drugs, each with multiple dose levels. It is as easy to implement as the 3+3 design, but yields superior performance compared to more complicated model-based designs.

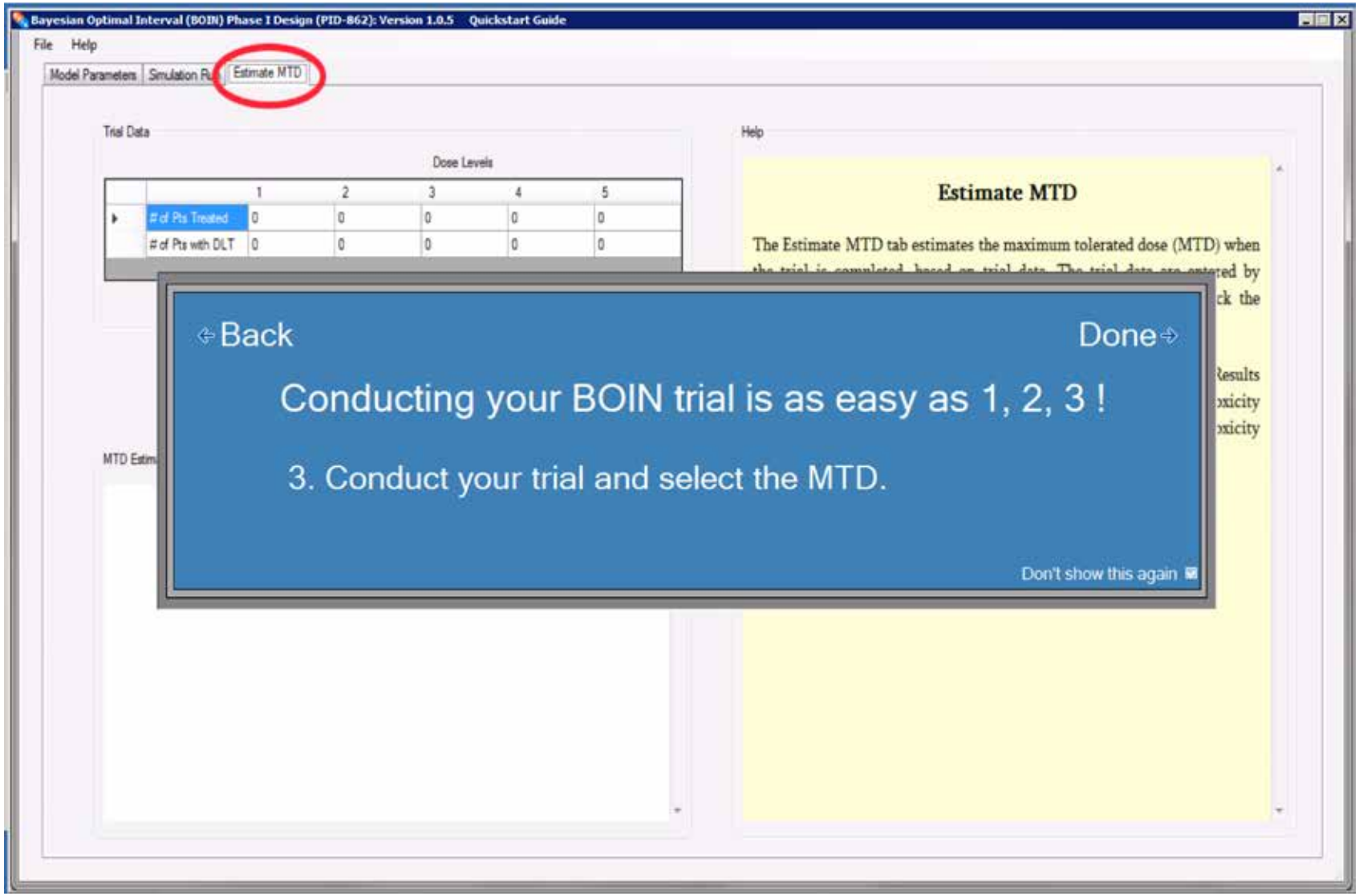

Biostatistics Software Dc
Secure | https://biostatistics.mdanderson.org/softwaredownload/
Quantitative Research Computing
Software Online Site
Contact Us
Home
THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Software Download Kiosk
17,000+ users
Click for interactive map
BOIN Design Desktop Program
Last Modified Date
Product Name
Brief Description
2017-06-09 BOIN Design Desktop Program Bayesian Optimal Interval (BOIN) design for phase I trials to find the maximum tolerated dose (MTD) for both single-agent and drug-combination trials
2017-01-18 One Arm Time to Event Simulator Design and simulate One-Arm Time-to-Event clinical trials using a Windows GUI
2017-01-13 Adaptive Randomization Outcome-adaptive randomization for clinical trials
2016-09-14 BMA CRM Dose-finding software using the Bayesian Model Averaging Continual Reassessment Method, including Data Augmentation
2016-06-28 UAROET Phase 1/II dose-finding with utility-based adaptive randomization and ordinal efficacy and toxicity.
2016-04-25 CATBUB Design Categorical Outcome Utility-Based Designs for Randomized Comparative Clinical Trials with Discrete Outcomes (formerly called 'BUB Design')
2016-04-20 U2OET Phase 1-II dose-pair-finding based on utilities of 4-level ordinal efficacy and toxicity.
2015-09-23 WFMM Wavelet-based functional mixed model software
2015-02-12 Beta Binomial Distribution Demo A learning tool to demonstrate a beta-binomial distribution prior being updated to become a posterior distribution
2014-08-27 Pinnacle A method for detection and quantification of protein spots from 2-D gel electrophoresis images.
2014-05-22 EffTox Phase 1/II dose-finding based on efficacy and toxicity
2014-04-01 Predictive Probabilities Predictive probability interim analysis of clinical trials
2013-11-26 Inequality Calculator Calculate the probability of one random variable being larger than another
2013-11-22 ParameterSolver Solve for distribution parameters for common distributions
2013-07-25 Multc Lean Monitoring toxicity and efficacy in phase II clinical trials
2013-01-09 Bayes Factor Binary A Bayesian hypothesis test-based method for clinical trials with single arm binary patient outcomes
2012-12-11 TTEDesigner Software for designing single arm safety monitoring trials with time-to-event endpoints
2012-10-05 Toxicity Probability Intervals Dose-finding based on toxicity probability intervals
2012-06-06 BlockARAND Block adaptive randomization

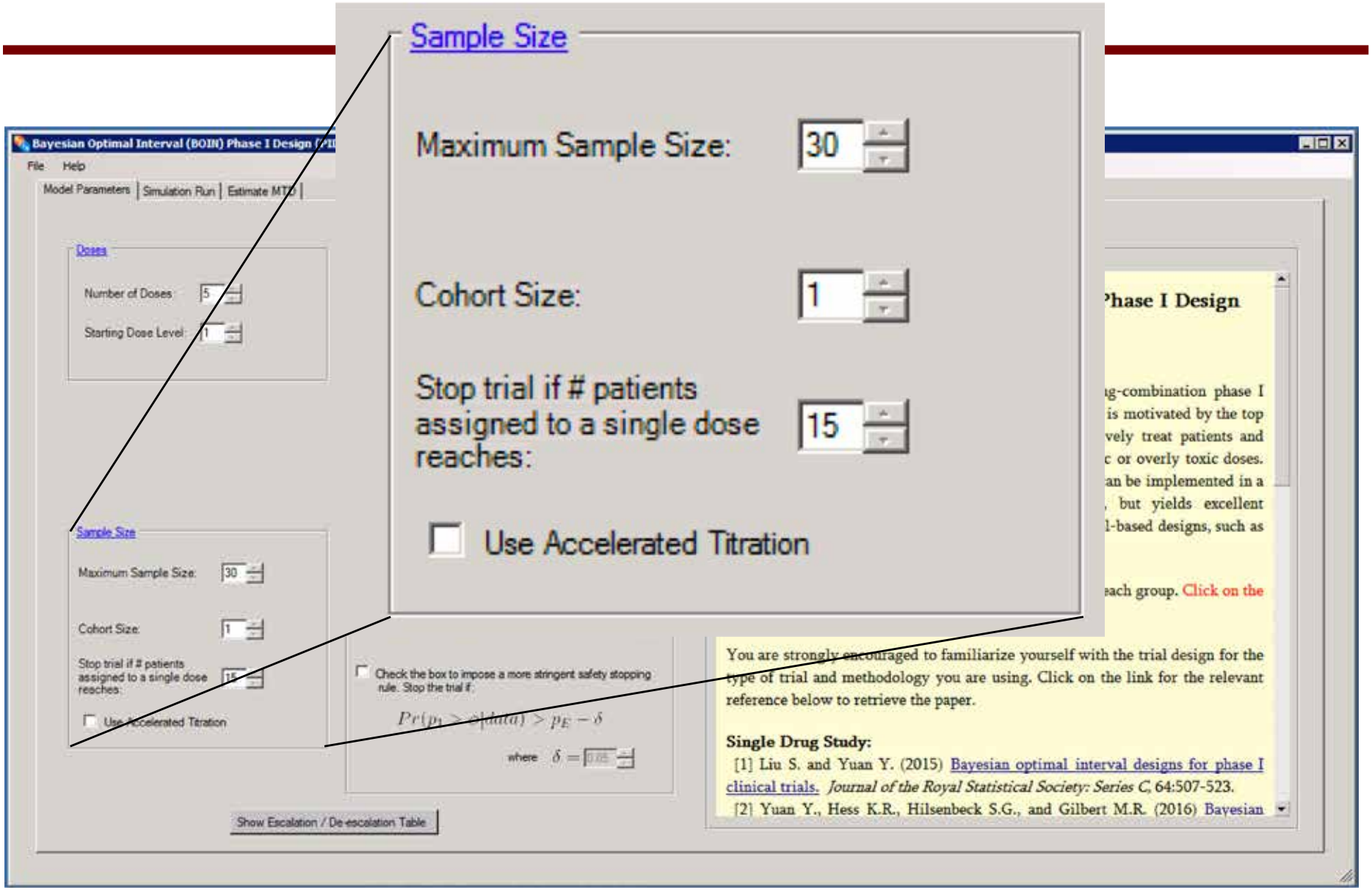

Quantitative Research Computing
Software Online Site
Contact Us
Home
THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Software Download Kiosk
19,800+ users
Click for interactive map
+
−
Who's Using Our Software?
Each Dot Represents the Location of One Person
(17,500 Are Currently Shown)
06 Apr 2016
Quantitative Research Computing
MD Anderson Cancer Center

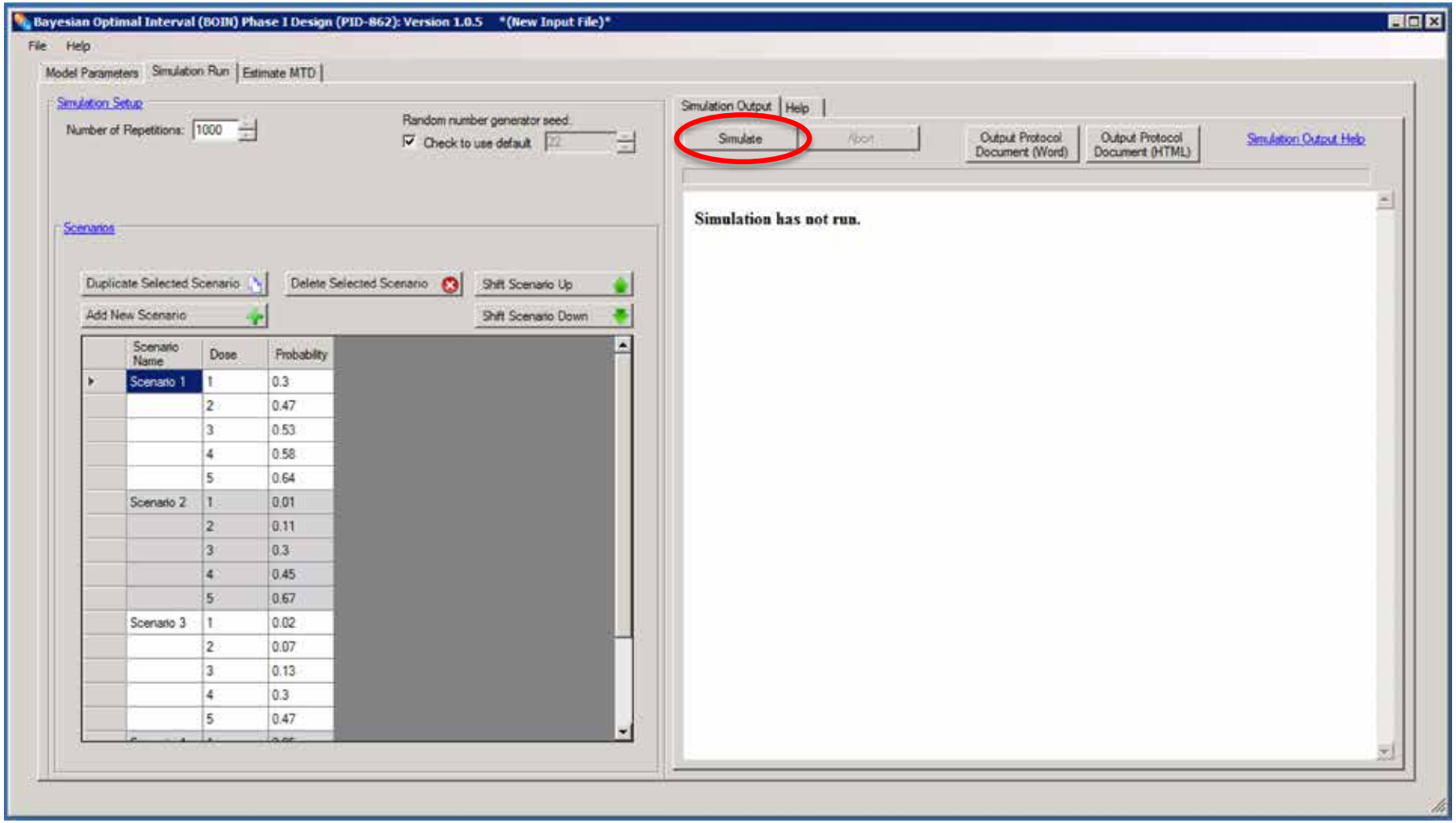

Bayesian Optimal Interval (BOIN) Phase I Design (PID-862): Version 1.0.5
Bayesian Optimal Interval (BOIN) Design
(Select your type of BOIN design)
BOIN
Find MTD for single-agent trials
BOIN is a novel model-assisted phase I trial design that is as easy to implement as the 3+3 design, but yields superior performance compared to more complicated model-based designs, such as CRM.
TITE-BOIN
Find MTD in trials with late-onset toxicity or fast accrual
Time-to-event BOIN (TITE-BOIN) allows for real-time dose assignment for new patients while some enrolled patients' toxicity data are still pending, thereby significantly shortening the trial duration. It is as easy to implement as the rolling 6 design, but yields much better performance.
BOIN Comb
Find MTD or MTD contour for combination trials
BOIN Comb handles combinations of two drugs, each with multiple dose levels. It is as easy to implement as the 3+3 design, but yields superior performance compared to more complicated model-based designs.

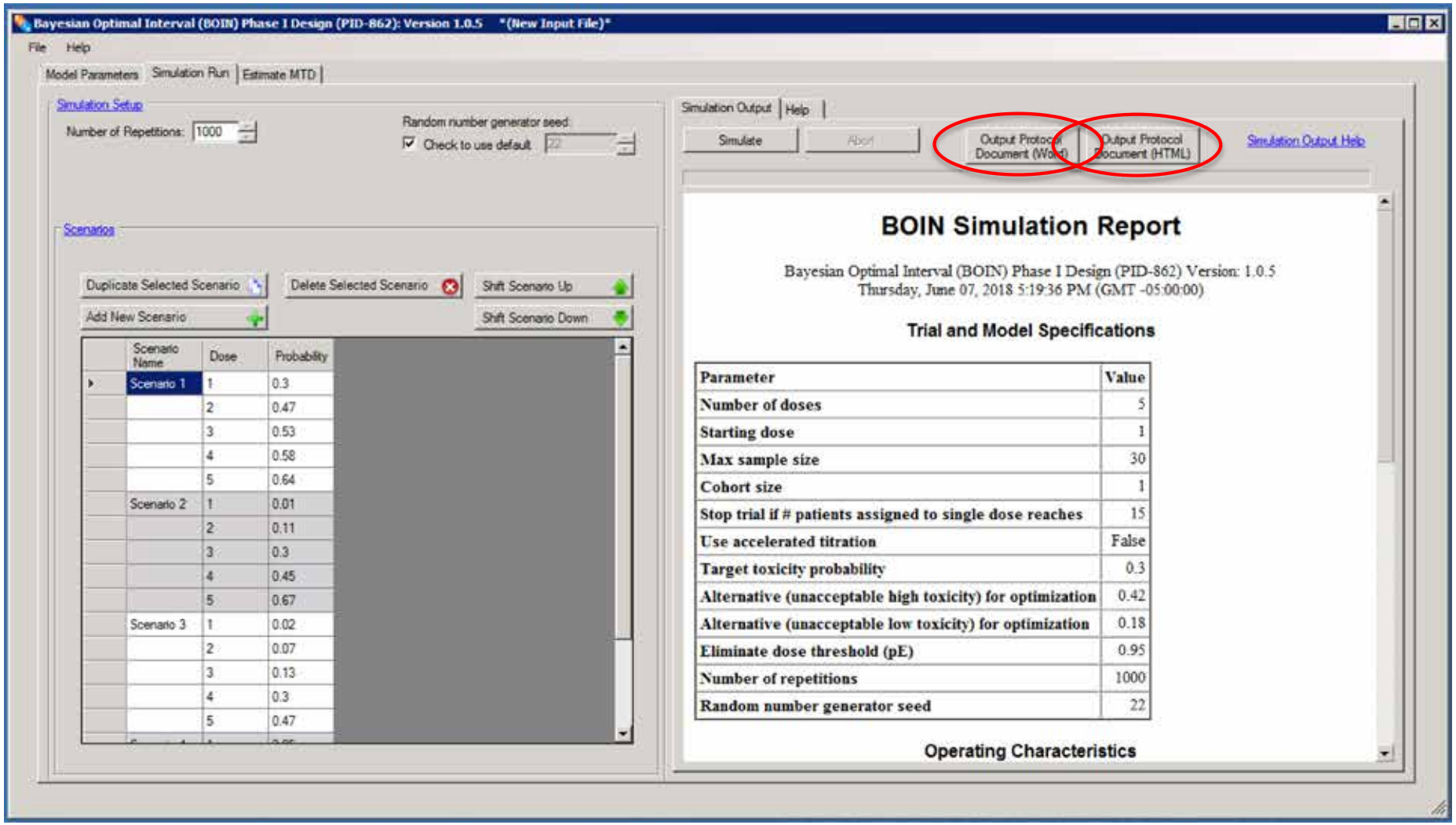

Bayesian Optimal Interval (BOIN) Phase I Design (PID-862): Version 1.0.5 Quickstart Guide
File Help
Model Parameters
Simulation Run
Estimate MTD
Doses
Number of Doses: 5
Starting Dose Level: 1
Target Probability
Target Toxicity Probability: $\phi = 0.30$
Use the default alternatives to minimize decision errors (recommended)
Help
Bayesian Optimal INterval (BOIN) Phase I Design
Overview
Next
Conducting your BOIN trial is as easy as 1, 2, 3 !
1. Enter your Model Parameters.
Don't show this again
Sample Size
Maximum San
Cohort Size:
Stop trial if # patients assigned to a single dose reaches: 15
Use Accelerated Titration
Check the box to impose a more stringent safety stopping rule. Stop the trial if:
$Pr(p_1 > \phi|data) > p_E - \delta$
where $\delta = 0.05$
Show Escalation / De-escalation Table
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


Bayesian Optimal Interval (BOIN) Phase I Design (PID-862): Version 1.0.5 Quickstart Guide
File Help
Model Parameter
Simulation Run
Estimate MTD
Simulation Setup
Number of Repetitions: 1000
Random number generator seed:
Check to use default
22
Simulation Output
Help
Simulate
Abort
Output Protocol Document (Word)
Output Protocol Document (HTML)
Simulation Output Help
Simulation has not run.
Scenarios
Duplicate Sel
Add New Scen
Back
Next
Conducting your BOIN trial is as easy as 1, 2, 3 !
2. Run simulations, get the operating characteristics, and produce your protocol template.
Don't show this again
4 0.45
5 0.67
Scenario 3 1 0.02
2 0.07
3 0.13
4 0.3
5 0.47


Bayesian Optimal Interval (BOIN) Phase I Design (PID-862): Version 1.0.5 Quickstart Guide
File Help
Model Parameters
Simulation Ru
Estimate MTD
Trial Data
Dose Levels
1 2 3 4 5
# of Pts Treated 0 0 0 0 0
# of Pts with DLT 0 0 0 0 0
Help
Estimate MTD
The Estimate MTD tab estimates the maximum tolerated dose (MTD) when
ed by
ck the
Results
oxicity
oxicity
MTD Estim
Back
Done
Conducting your BOIN trial is as easy as 1, 2, 3 !
3. Conduct your trial and select the MTD.
Don't show this again


Sample Size
Maximum Sample Size:
30
Cohort Size:
1
Stop trial if # patients assigned to a single dose reaches:
15
Use Accelerated Titration
Bayesian Optimal Interval (BOIN) Phase I Design
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
Use Accelerated Titration
Check the box to impose a more stringent safety stopping rule. Stop the trial if:
$Pr(p_1 > p_E|data) > p_E - \delta$
where $\delta =$
Show Escalation / De-escalation Table
Phase I Design
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


Bayesian Optimal Interval (BOIN) Phase I Design (PID-862): Version 1.0.5 *(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
72
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
Simulation Output
Help
Simulate
Abort
Output Protocol Document (Word)
Output Protocol Document (HTML)
Simulation Output Help
Simulation has not run.


Bayesian Optimal Interval (BOIN) Phase I Design (PID-862): Version 1.0.5 *(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
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
Simulation Output
Help
Simulate
Abort
Output Protocol Document (Word)
Output Protocol Document (HTML)
Simulation Output Help
BOIN Simulation Report
Bayesian Optimal Interval (BOIN) Phase I Design (PID-862) Version: 1.0.5
Thursday, June 07, 2018 5:19:36 PM (GMT -05:00:00)
Trial and Model Specifications
Parameter
Value
Number of doses
5
Starting dose
1
Max sample size
30
Cohort size
1
Stop trial if # patients assigned to single dose reaches
15
Use accelerated titration
False
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
Number of repetitions
1000
Random number generator seed
22
Operating Characteristics

Template for Protocol Preparation

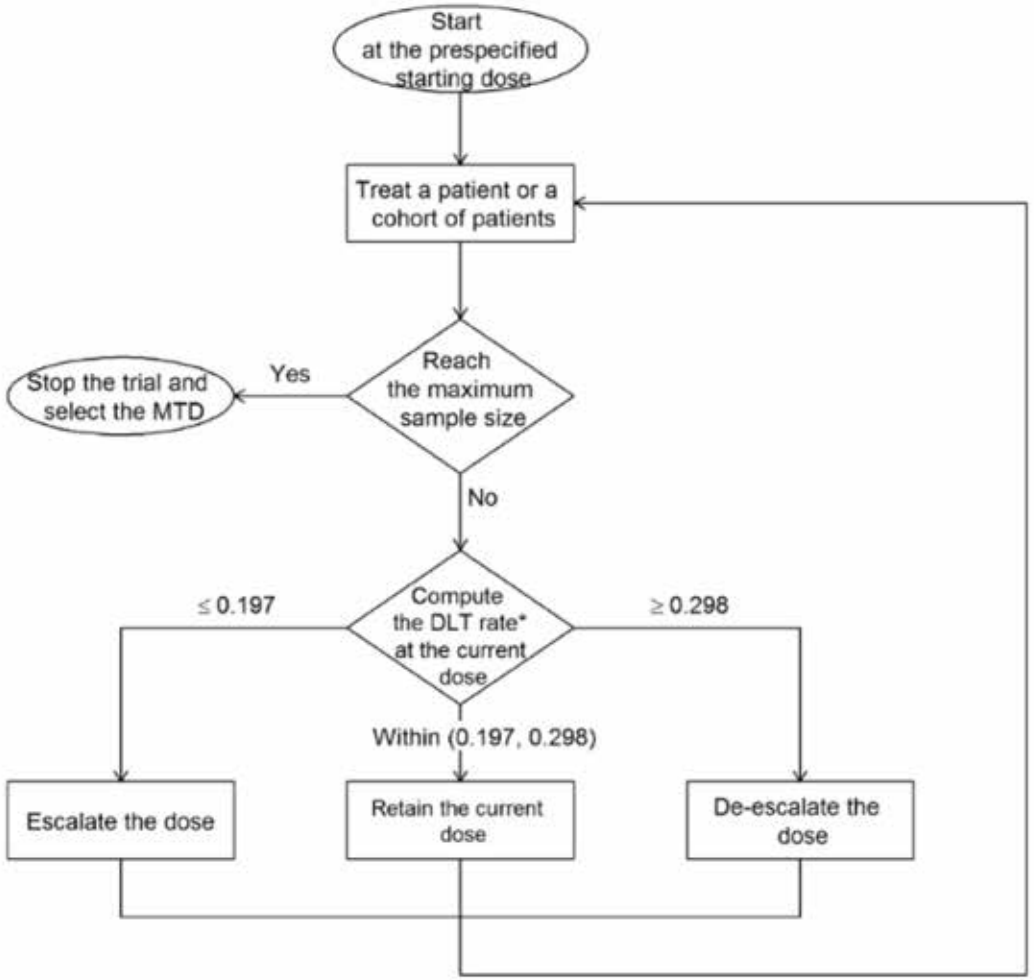
We will employ the Bayesian optimal interval (BOIN) design (Liu and Yuan, 2015) to find the MTD. The BOIN design is implemented in a simple way similar to the traditional 3+3 design, but is more flexible and possesses superior operating characteristics that are comparable to those of the more complex model-based designs, such as the continual reassessment method (CRM).

The target toxicity rate for the MTD is 0.2 and the maximum sample size is 20. We will enroll and treat patients in cohorts of size 2. The trial design is described as follows:

1. Patients in the first cohort are treated at dose level 1.
2. To assign a dose to the next cohort of patients, we conduct dose escalation/de-escalation according to the rule displayed in Table 1. When using Table 1, please note the following
    a. "Eliminate" means that we eliminate the current and higher doses from the trial to prevent treating any future patients at these doses because they are overly toxic.
    b. When we eliminate a dose, we automatically de-escalate the dose to the next lower level. When the lowest dose is eliminated, we stop the trial for safety. In this case, no dose should be selected as the MTD.
    c. If none of the actions (i.e., escalation, de-escalation or elimination) is triggered, we treat the new patients at the current dose.
    d. If the current dose is the lowest dose and the rule indicates dose de-escalation, we will treat the new patients at the lowest dose unless the number of DLTs reaches the elimination boundary, at which point we will terminate the trial for safety.
    e. If the current dose is the highest dose and the rule indicates dose escalation, we will treat the new patients at the highest dose.
3. Repeat step 2 until the maximum sample size of 20 is reached or the trial is stopped.

Table 1. Dose escalation/de-escalation rule for the BOIN design.

Actions	The number of patients treated at the current dose																			
	1	**2**	3	**4**	5	**6**	7	**8**	9	**10**	11	**12**	13	**14**	15	**16**	17	**18**	19	**20**
Escalate if # of DLT <=	0	**0**	0	**0**	0	**0**	1	**1**	1	**1**	1	**1**	2	**2**	2	**2**	2	**2**	2	**3**
De-escalate if # of DLT >=	1	**1**	1	**1**	2	**2**	2	**2**	3	**3**	3	**3**	4	**4**	4	**4**	5	**5**	5	**5**
Eliminate if # of DLT >=	NA	**NA**	2	**3**	3	**3**	4	**4**	4	**5**	5	**5**	5	**6**	6	**6**	7	**7**	7	**7**



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

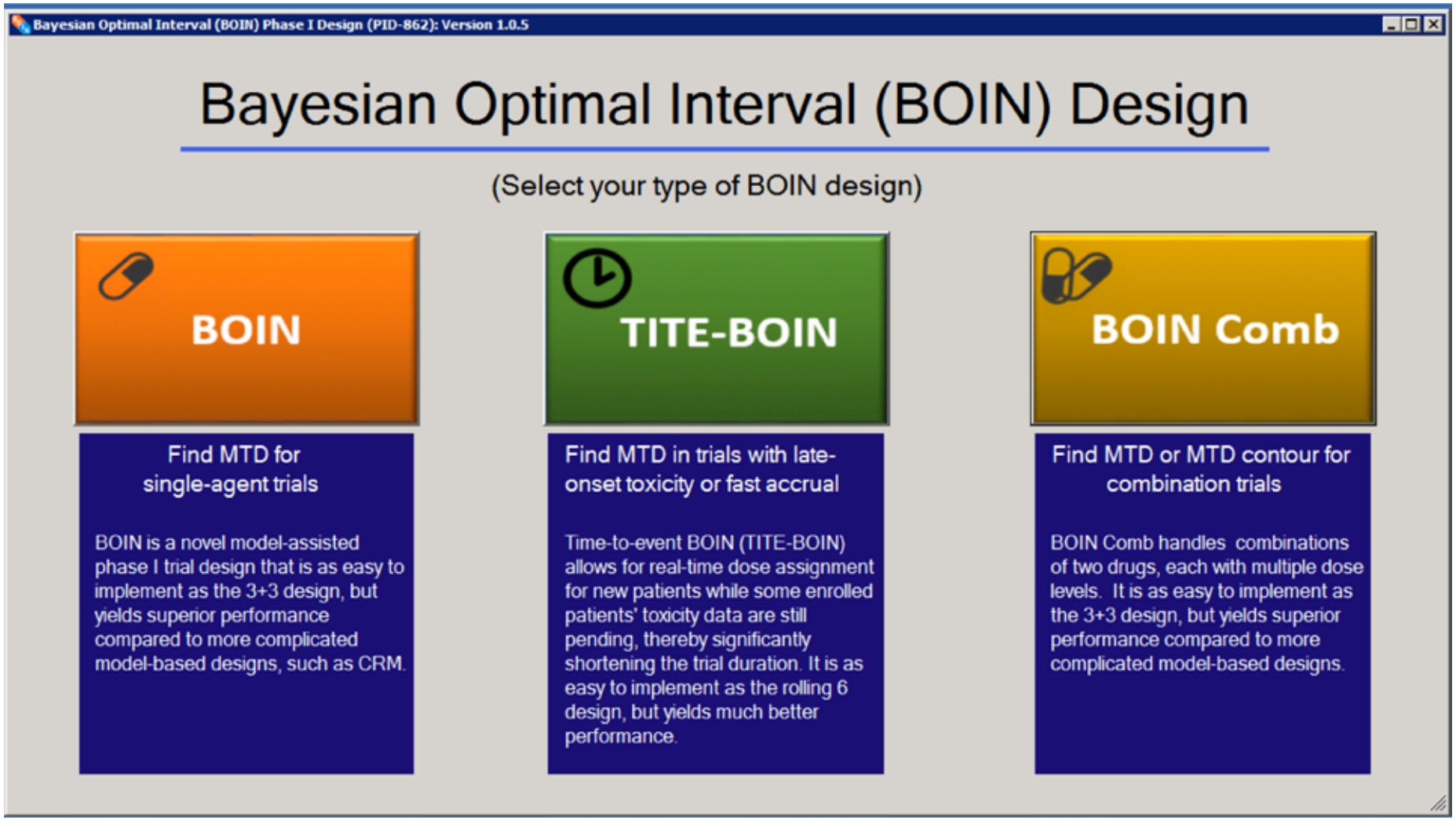
Figure 1. Flowchart for trial conduct using the BOIN design.

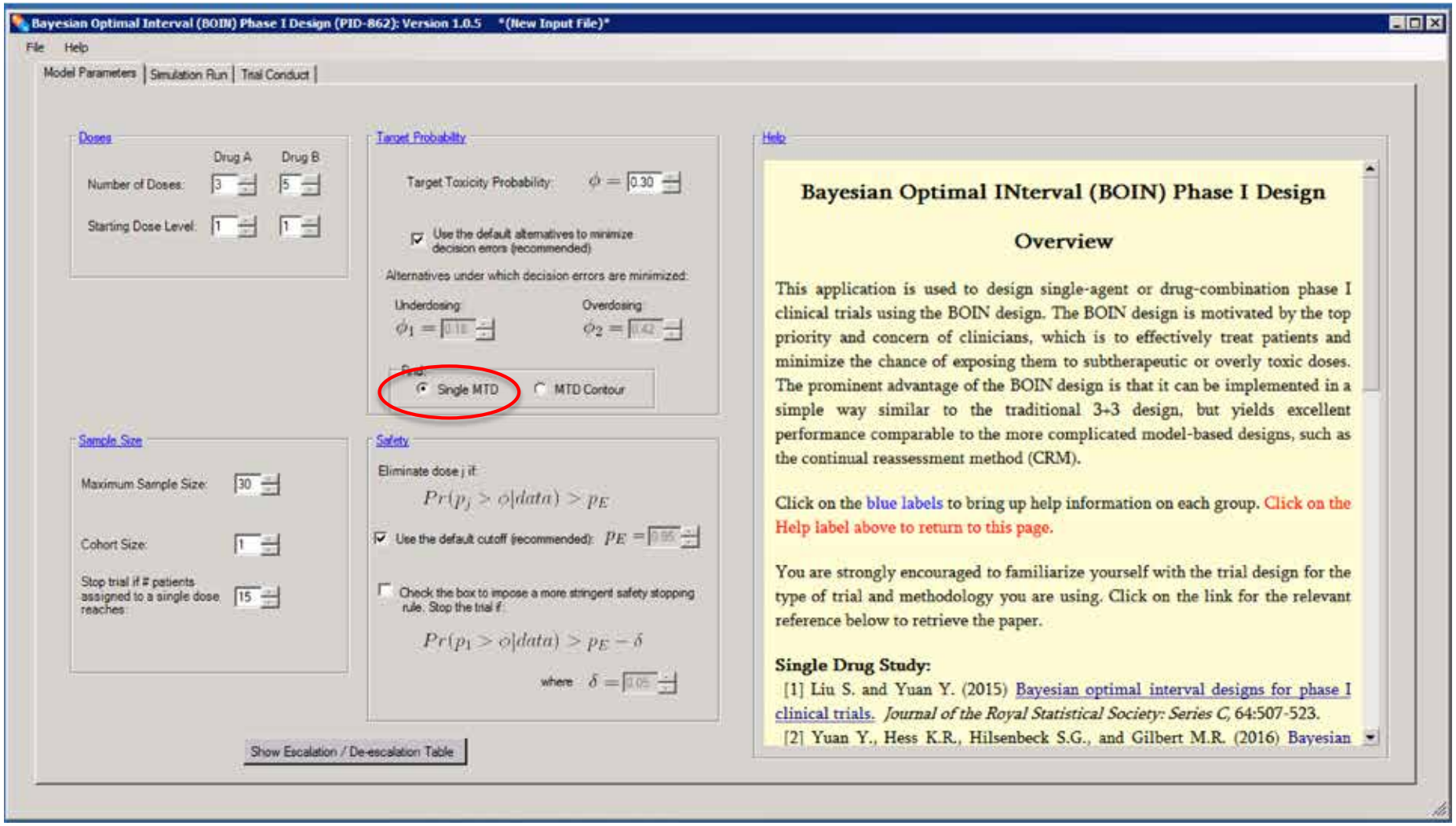
Operating characteristics

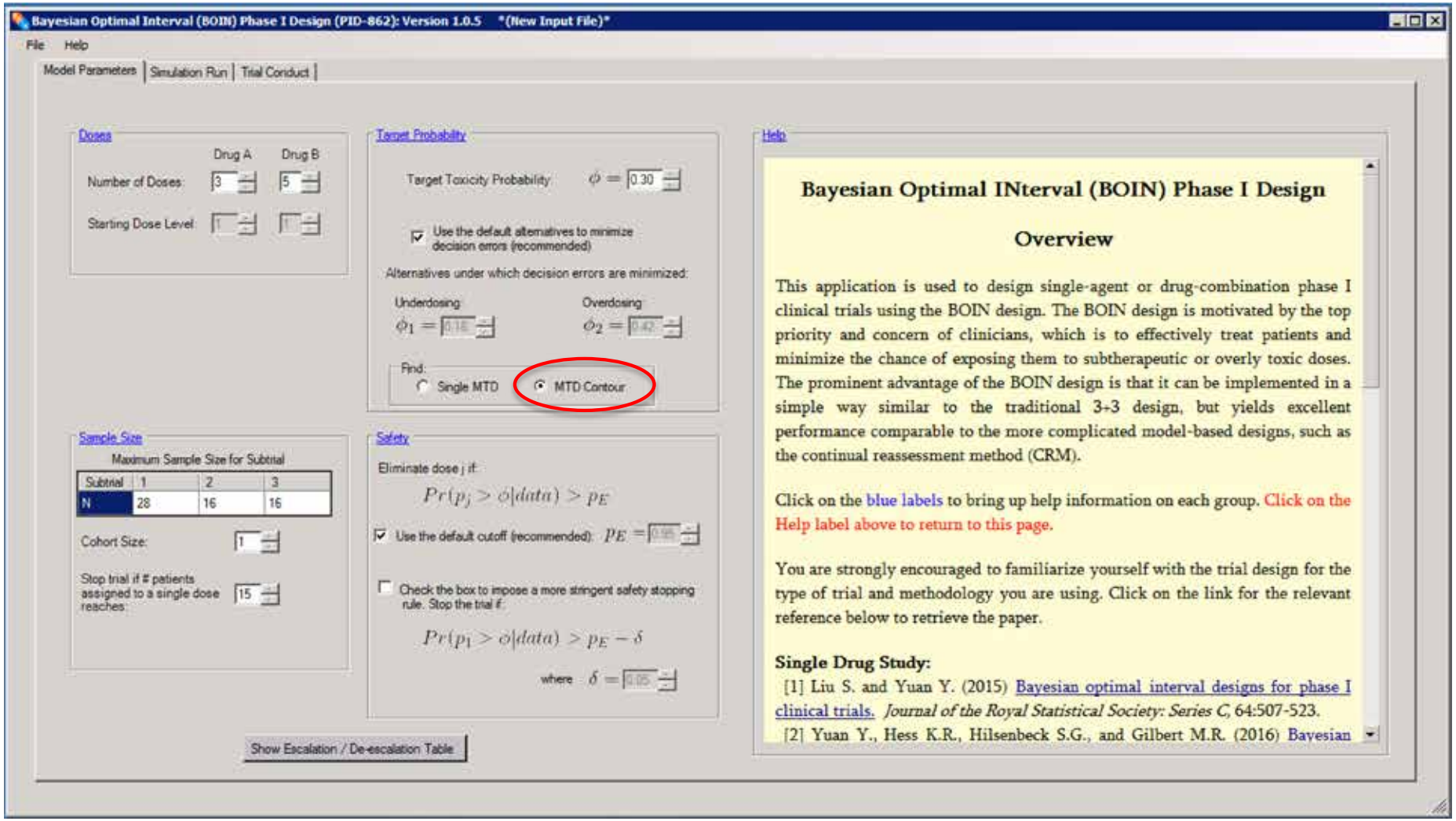
Table 2 shows the operating characteristics of the trial design based on 5000 simulations of the trial using the BOIN Design Desktop Program (Venier et al., 2017). The operating characteristics show that the design selects the true MTD, if any, with high probability and allocates more patients to the dose levels with the DLT rate closest to the target of 0.25.

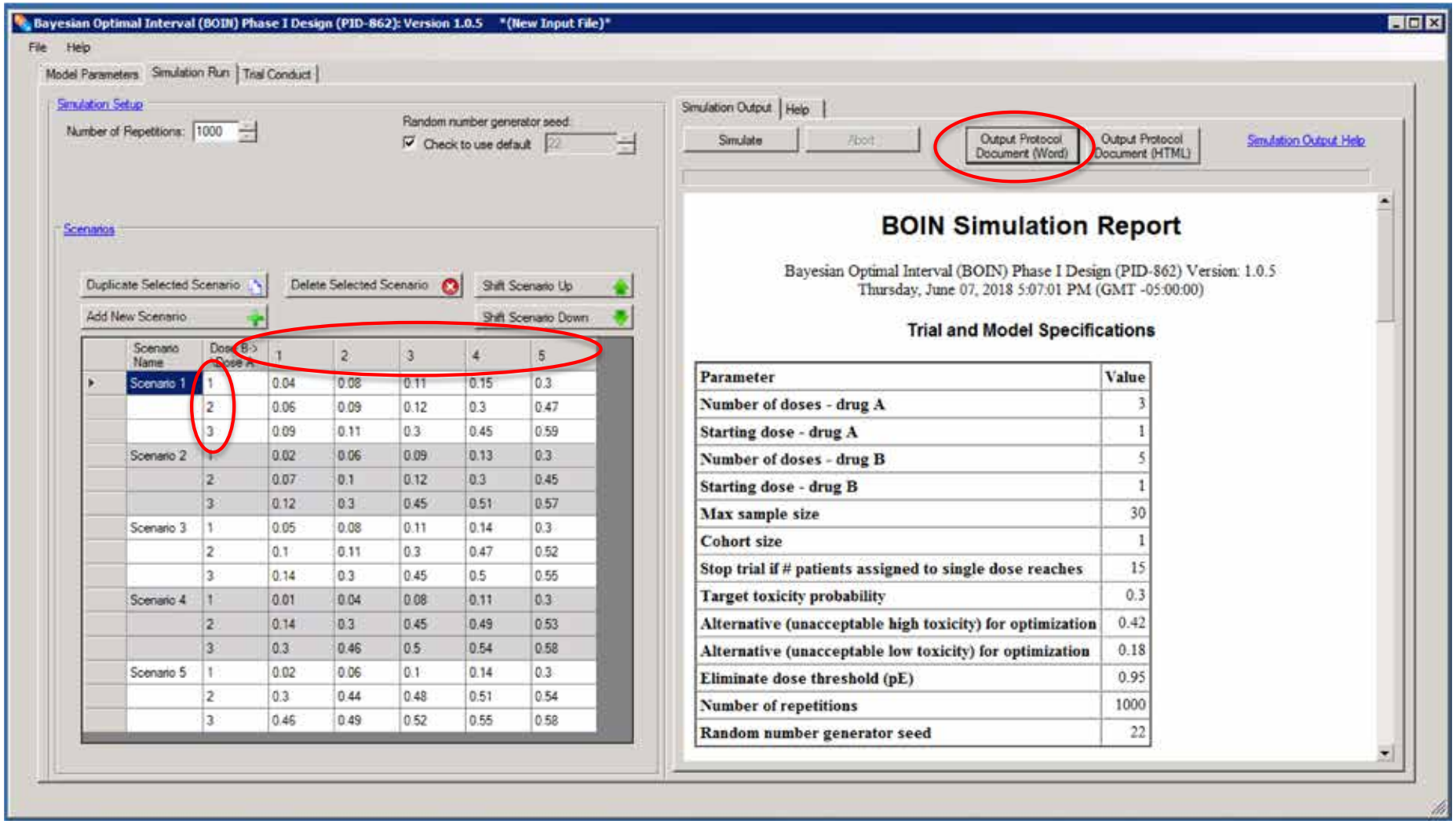
Table 2. Operating Characteristics of the BOIN design

	Dose Level				Number of Patients	% Early Stopping
	1	2	3	4		
Scenario 1						
True DLT Rate	0.25	0.42	0.50	0.59		
Selection %	70.9	16.9	1.5	0.1		10.5
# Pts Treated	13.6	7.7	1.4	0.2	22.94	
Scenario 2						
True DLT Rate	0.10	0.25	0.40	0.62		
Selection %	21.8	60.3	17.1	0.6		0.2
# Pts Treated	6.5	11.8	4.9	0.8	23.97	
Scenario 3						
True DLT Rate	0.02	0.10	0.25	0.42		
Selection %	0.5	24.7	60.7	14.1		0.0


Bayesian Optimal Interval (BOIN) Phase I Design (PID-862): Version 1.0.5
Bayesian Optimal Interval (BOIN) Design
(Select your type of BOIN design)
BOIN
Find MTD for single-agent trials
BOIN is a novel model-assisted phase I trial design that is as easy to implement as the 3+3 design, but yields superior performance compared to more complicated model-based designs, such as CRM.
TITE-BOIN
Find MTD in trials with late-onset toxicity or fast accrual
Time-to-event BOIN (TITE-BOIN) allows for real-time dose assignment for new patients while some enrolled patients' toxicity data are still pending, thereby significantly shortening the trial duration. It is as easy to implement as the rolling 6 design, but yields much better performance.
BOIN Comb
Find MTD or MTD contour for combination trials
BOIN Comb handles combinations of two drugs, each with multiple dose levels. It is as easy to implement as the 3+3 design, but yields superior performance compared to more complicated model-based designs.


Bayesian Optimal Interval (BOIN) Phase I Design (PID-862): Version 1.0.5 *(New Input File)*
File Help
Model Parameters | Simulation Run | Trial Conduct
Doses
Drug A Drug B
Number of Doses: 3 5
Starting Dose Level: 1 1
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: $\phi_2 = 0.42$
Single MTD
MTD Contour
Sample Size
Maximum Sample Size: 30
Cohort Size: 1
Stop trial if # patients assigned to a single dose reaches: 15
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 $\delta = 0.05$
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


Bayesian Optimal Interval (BOIN) Phase I Design (PID-862): Version 1.0.5 *(New Input File)*
File
Help
Model Parameters
Simulation Run
Trial Conduct
Doses
Drug A
Drug B
Number of Doses:
3
5
Starting Dose Level:
1
1
Target Probability
Target Toxicity Probability: ϕ = 0.30
Use the default alternatives to minimize decision errors (recommended)
Alternatives under which decision errors are minimized:
Underdosing: ϕ_1 = 0.18
Overdosing: ϕ_2 = 0.42
Find:
Single MTD
MTD Contour
Sample Size
Maximum Sample Size for Subtrial
Subtrial 1 2 3
N 28 16 16
Cohort Size:
1
Stop trial if # patients assigned to a single dose reaches:
15
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 δ = 0.05
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


Bayesian Optimal Interval (BOIN) Phase I Design (PID-862): Version 1.0.5 *(New Input File)*
File Help
Model Parameters Simulation Run Trial Conduct
Simulation Setup
Number of Repetitions: 1000
Random number generator seed:
Check to use default 22
Scenarios
Duplicate Selected Scenario
Delete Selected Scenario
Shift Scenario Up
Add New Scenario
Shift Scenario Down
Scenario Name
Dose: B-> Dose A
1 2 3 4 5
Scenario 1 1 0.04 0.08 0.11 0.15 0.3
2 0.06 0.09 0.12 0.3 0.47
3 0.09 0.11 0.3 0.45 0.59
Scenario 2 1 0.02 0.06 0.09 0.13 0.3
2 0.07 0.1 0.12 0.3 0.45
3 0.12 0.3 0.45 0.51 0.57
Scenario 3 1 0.05 0.08 0.11 0.14 0.3
2 0.1 0.11 0.3 0.47 0.52
3 0.14 0.3 0.45 0.5 0.55
Scenario 4 1 0.01 0.04 0.08 0.11 0.3
2 0.14 0.3 0.45 0.49 0.53
3 0.3 0.46 0.5 0.54 0.58
Scenario 5 1 0.02 0.06 0.1 0.14 0.3
2 0.3 0.44 0.48 0.51 0.54
3 0.46 0.49 0.52 0.55 0.58
Simulation Output Help
Simulate Abort
Output Protocol Document (Word)
Output Protocol Document (HTML)
Simulation Output Help
BOIN Simulation Report
Bayesian Optimal Interval (BOIN) Phase I Design (PID-862) Version: 1.0.5
Thursday, June 07, 2018 5:07:01 PM (GMT -05:00:00)
Trial and Model Specifications
Parameter Value
Number of doses - drug A 3
Starting dose - drug A 1
Number of doses - drug B 5
Starting dose - drug B 1
Max sample size 30
Cohort size 1
Stop trial if # patients assigned to single dose reaches 15
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
Number of repetitions 1000
Random number generator seed 22

Template for Drug-Combination Protocol Preparation

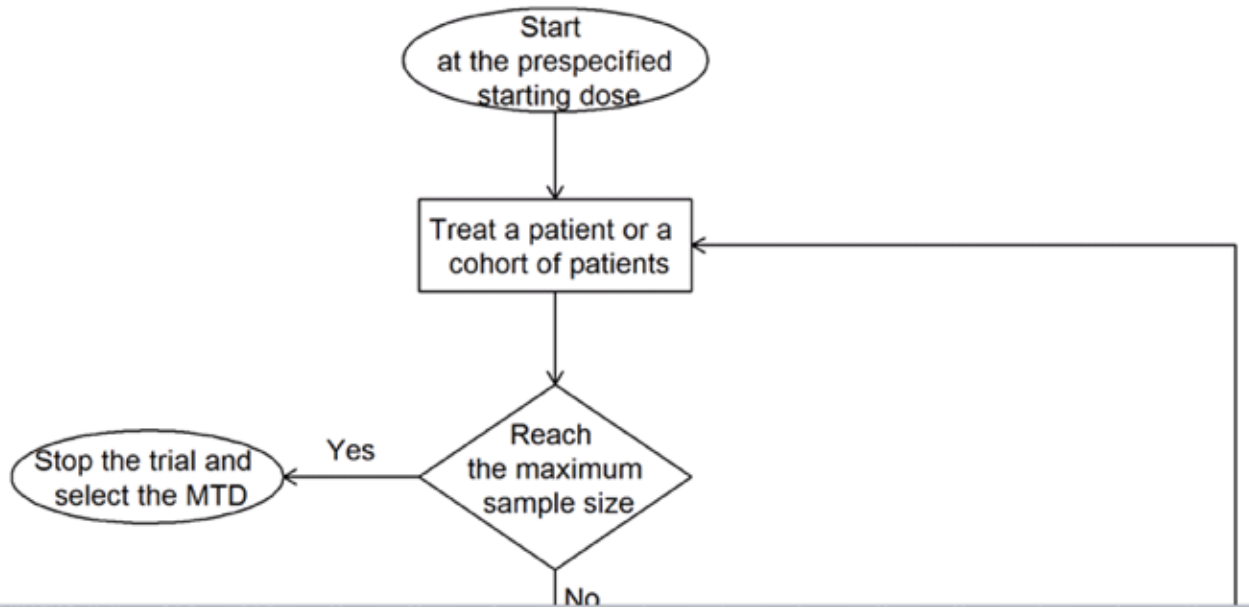
We will employ the Bayesian optimal interval (BOIN) design (Liu and Yuan, 2015; Lin and Yin, 2015) to find the MTD. The BOIN design is a novel Bayesian dose-finding method that optimizes patient treatment ethics by minimizing the chance of exposing patients to sub-therapeutic and overly toxic doses. The BOIN design 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. This trial was designed and will be conducted using the BOIN Design Desktop Program v1.0.5 (Venier et al., 2018).

The target toxicity rate for the MTD is $\phi = 0.3$ and the maximum sample size is 30. We will enroll and treat patients in cohorts of size 1. Let (j, k) denote the combination of jth dose level of agent A and kth dose level of agent B. The trial design is illustrated in Figure 1 and described as follows:

1. Patients in the first cohort are treated at the lowest dose combination (1, 1).
2. Suppose that the current dose is (j, k). To assign a dose to the next cohort of patients, conduct dose escalation/de-escalation according to the rule displayed in Table 1, which minimizes the probability of incorrect dose assignment. Please note the following concerning this table:
    a. "Eliminate" means the current and higher doses, i.e., the dose set $\{(j^*, k^*); j^* \geq j$ and $k^* \geq k\}$, are eliminated from the trial to prevent treating any future patients at these doses because they are overly toxic.
    b. When a dose is eliminated, the dose is automatically de-escalated as described below. When the lowest dose (1, 1) is eliminated, the trial is stopped for safety. In this case, no dose should be selected as the MTD.
    c. When the rule indicates dose de-escalation, de-escalate to $(j-1, k)$ or $(j, k-1)$, whichever has the highest posterior probability that the true toxicity rate is located between the de-escalation and escalation boundaries displayed in Table 1 (i.e., having an acceptable toxicity rate). When $(j-1, k)$ and $(j, k-1)$ have the

Table 1. Dose escalation/de-escalation rule for the BOIN design.

Actions	The number of patients treated **at the current dose**														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Escalate if # of DLT <=	0	0	0	0	1	1	1	1	2	2	2	2	3	3	3
De-escalate if # of DLT >=	1	1	2	2	2	3	3	3	4	4	4	5	5	6	6
Eliminate if # of DLT >=	NA	NA	3	3	4	4	5	5	5	6	6	7	7	8	8



Operating characteristics

Table 2 shows the operating characteristics of the proposed design for this trial with 5 scenarios involving various numbers and locations for the MTDs. These operating characteristics are based on 1000 simulations of the trial using the BOIN Design Desktop Program (Venier et al., 2018). The operating characteristics show that the design selects one of the true MTD(s), if any, with high probability and allocates more patients to the dose levels with the DLT rate closest to the target of 0.3.

Table 2. Operating Characteristics of the BOIN design

Scenario 1

	Dose Level of Drug B														
	True DLT Rate					Selection %					# Pts Treated				
	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
1†	0.04	0.08	0.11	0.15	0.30	0.0	0.4	1.1	3.7	7.4	1.3	0.7	0.5	0.8	1.0
2†	0.06	0.09	0.12	0.30	0.47	0.5	1.1	6.3	16.3	6.1	0.6	0.9	2.1	2.9	1.8
3†	0.09	0.11	0.30	0.45	0.59	0.5	10.5	32.7	12.5	0.9	0.5	2.7	6.2	4.7	2.1

† Dose Level of Drug A

Average Number of Patients: 28.8

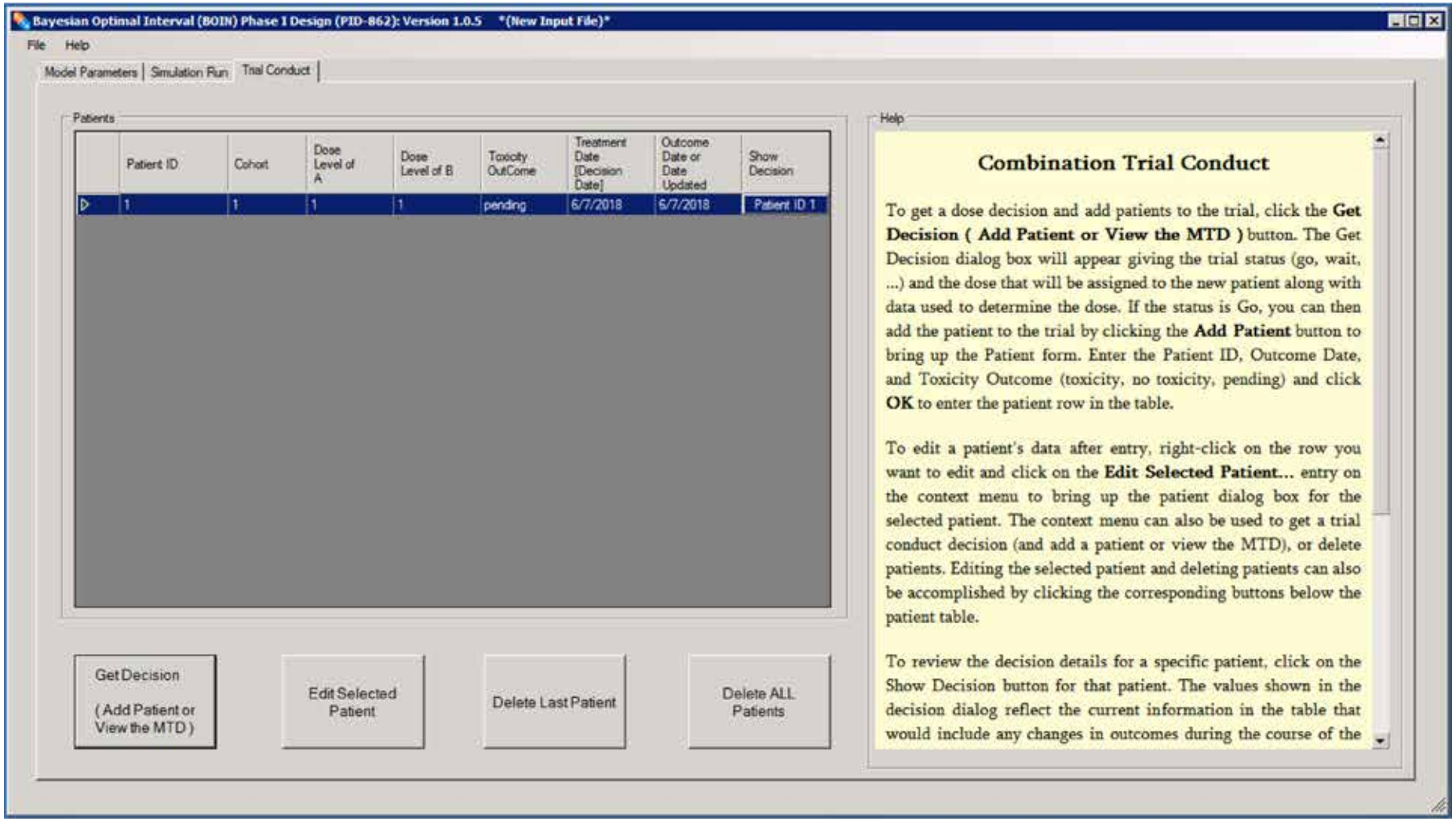
Selection Percentage of MTD: 56.4

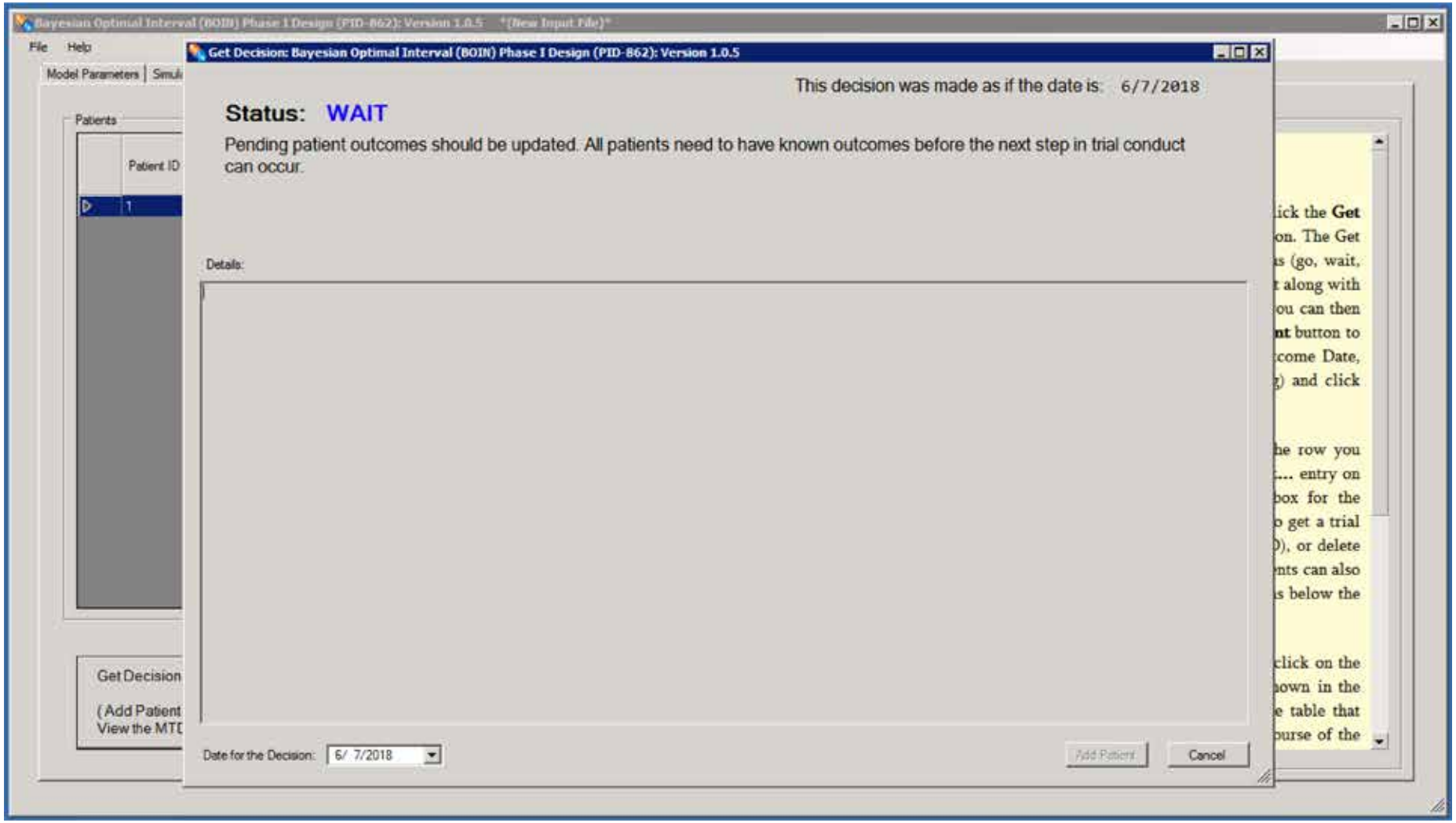
Percentage of Patients Treated at MTD: 33.6

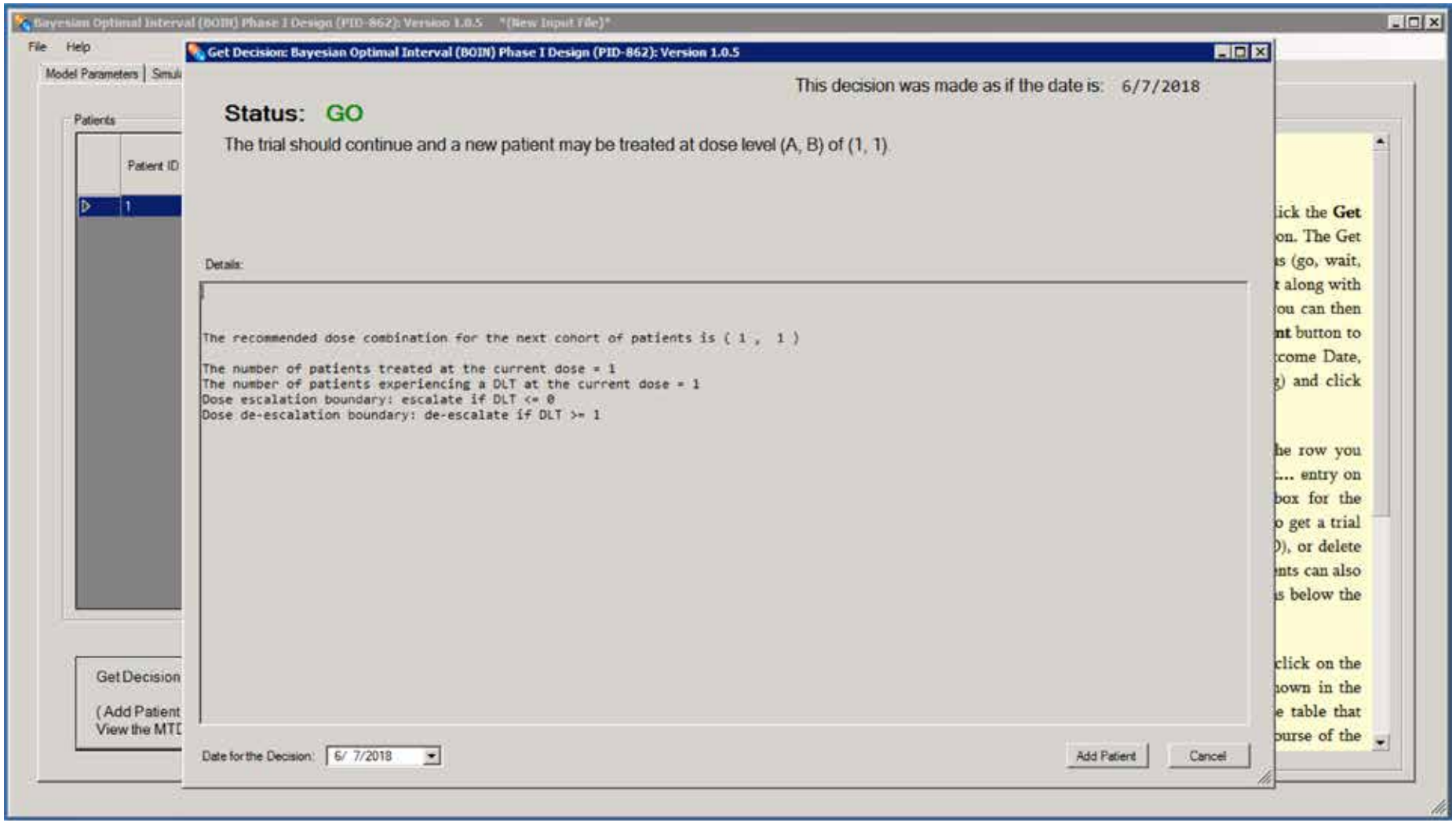
Percentage of Early Stopping Due to Toxicity: 0.0

Scenario 2

	Dose Level of Drug B														
	True DLT Rate					Selection %					# Pts Treated				
	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5

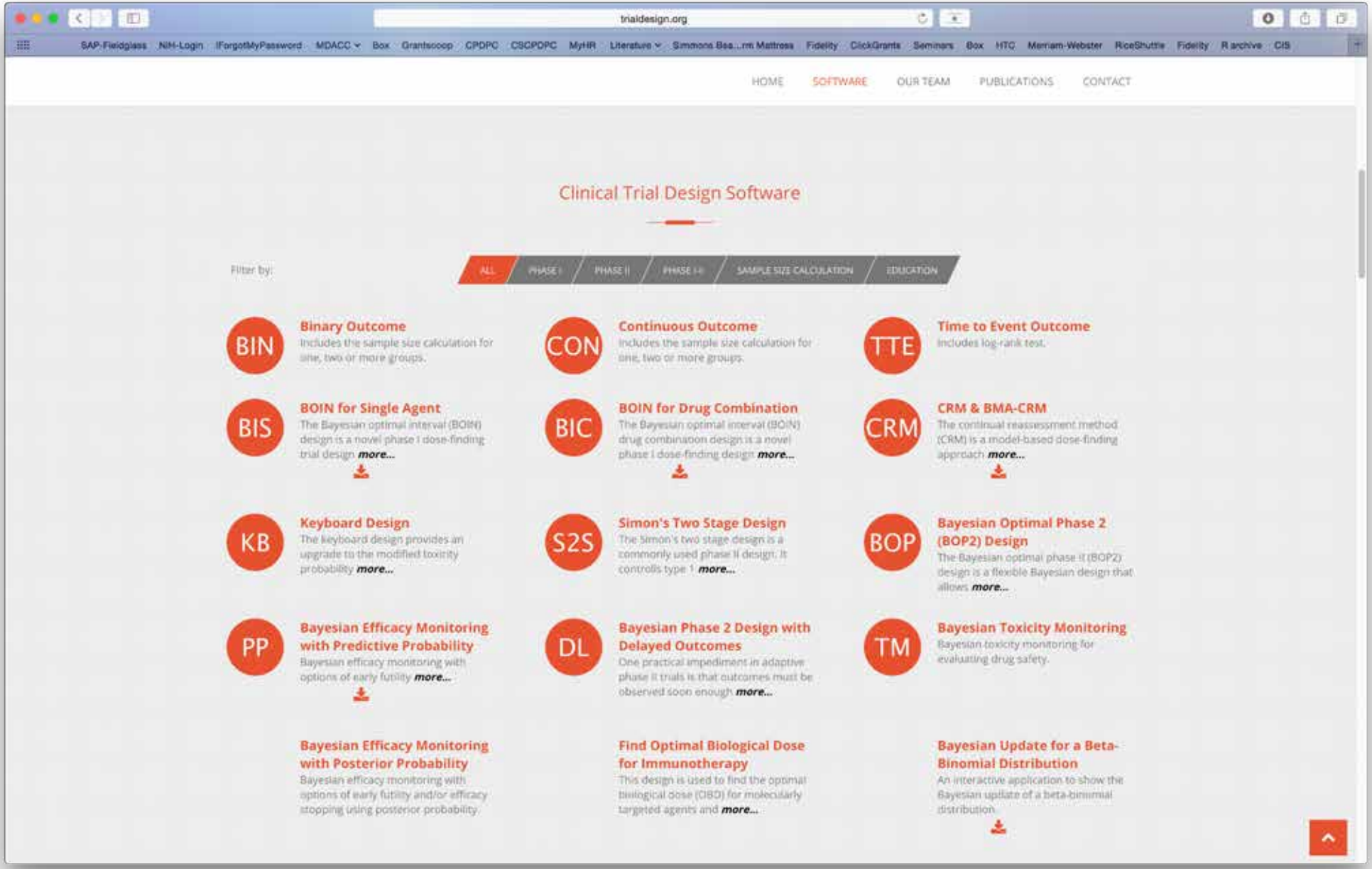

Bayesian Optimal Interval (BOIN) Phase I Design (PID-862): Version 1.0.5 *(New Input File)*
File
Help
Model Parameters
Simulation Run
Trial Conduct
Patients
Patient ID
Cohort
Dose Level of A
Dose Level of B
Toxicity OutCome
Treatment Date [Decision Date]
Outcome Date or Date Updated
Show Decision
1
1
1
1
pending
6/7/2018
6/7/2018
Patient ID 1
Get Decision
(Add Patient or View the MTD)
Edit Selected Patient
Delete Last Patient
Delete ALL Patients
Help
Combination Trial Conduct
To get a dose decision and add patients to the trial, click the Get Decision (Add Patient or View the MTD) button. The Get Decision dialog box will appear giving the trial status (go, wait, ...) and the dose that will be assigned to the new patient along with data used to determine the dose. If the status is Go, you can then add the patient to the trial by clicking the Add Patient button to bring up the Patient form. Enter the Patient ID, Outcome Date, and Toxicity Outcome (toxicity, no toxicity, pending) and click OK to enter the patient row in the table.
To edit a patient's data after entry, right-click on the row you want to edit and click on the Edit Selected Patient... entry on the context menu to bring up the patient dialog box for the selected patient. The context menu can also be used to get a trial conduct decision (and add a patient or view the MTD), or delete patients. Editing the selected patient and deleting patients can also be accomplished by clicking the corresponding buttons below the patient table.
To review the decision details for a specific patient, click on the Show Decision button for that patient. The values shown in the decision dialog reflect the current information in the table that would include any changes in outcomes during the course of the


Bayesian Optimal Interval (BOIN) Phase I Design (PID-862): Version 1.0.5 *(New Input File)*
File
Help
Model Parameters
Patients
Patient ID
1
Get Decision
(Add Patient
View the MTD
Get Decision: Bayesian Optimal Interval (BOIN) Phase I Design (PID-862): Version 1.0.5
This decision was made as if the date is: 6/7/2018
Status: WAIT
Pending patient outcomes should be updated. All patients need to have known outcomes before the next step in trial conduct can occur.
Details:
Date for the Decision: 6/ 7/2018
Add Patient
Cancel

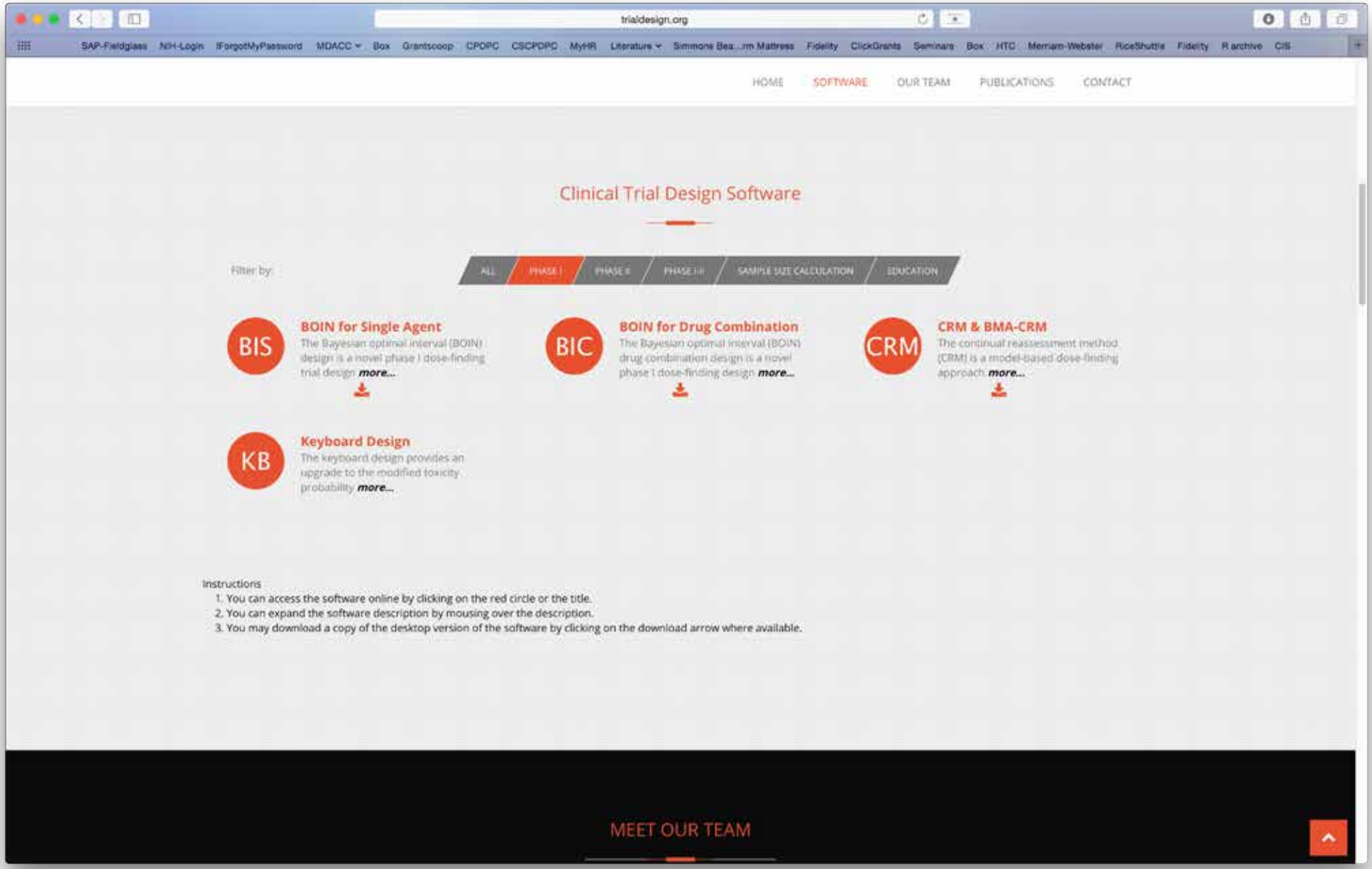

Bayesian Optimal Interval (BOIN) Phase I Design (PID-862): Version 1.0.5 *(New Input File)*
File Help
Model Parameters
Patients
Patient ID
1
Get Decision
(Add Patient
View the MTD
Get Decision: Bayesian Optimal Interval (BOIN) Phase I Design (PID-862): Version 1.0.5
This decision was made as if the date is: 6/7/2018
Status: GO
The trial should continue and a new patient may be treated at dose level (A, B) of (1, 1)
Details:
The recommended dose combination for the next cohort of patients is (1 , 1)
The number of patients treated at the current dose = 1
The number of patients experiencing a DLT at the current dose = 1
Dose escalation boundary: escalate if DLT <= 0
Dose de-escalation boundary: de-escalate if DLT >= 1
Date for the Decision: 6/ 7/2018
Add Patient
Cancel

www.trialdesign.org

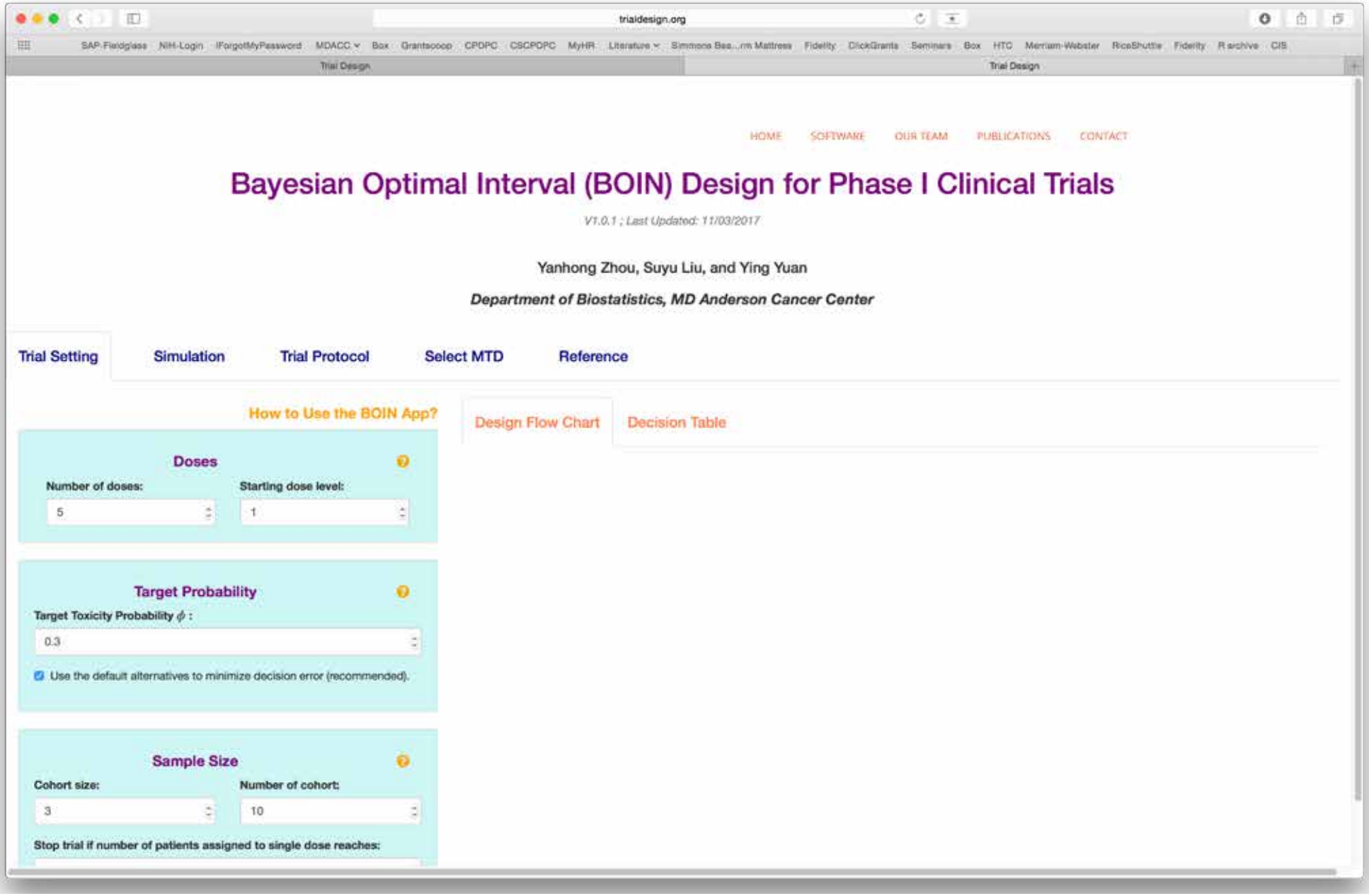
www.trialdesign.org



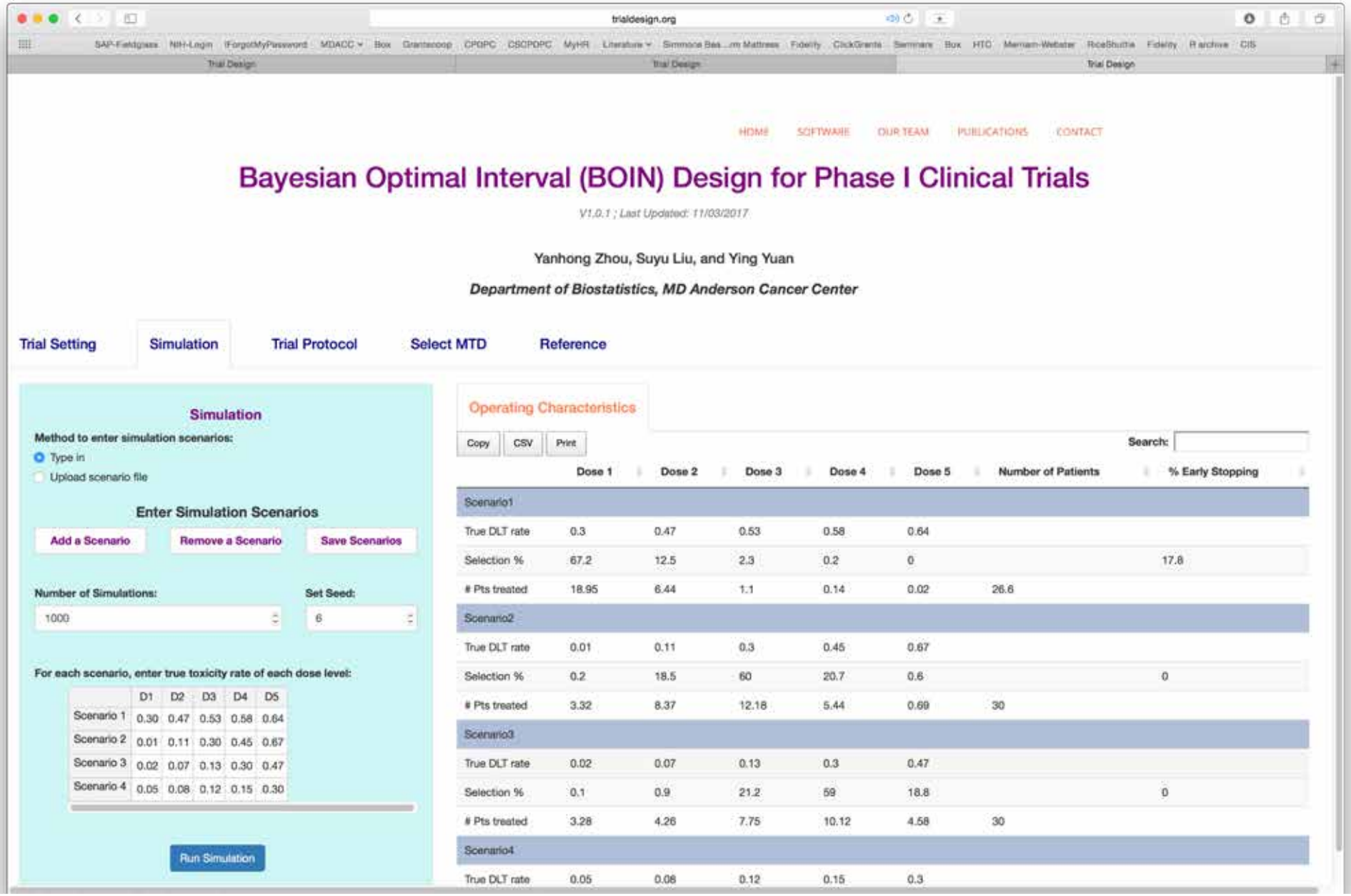
www.trialdesign.org



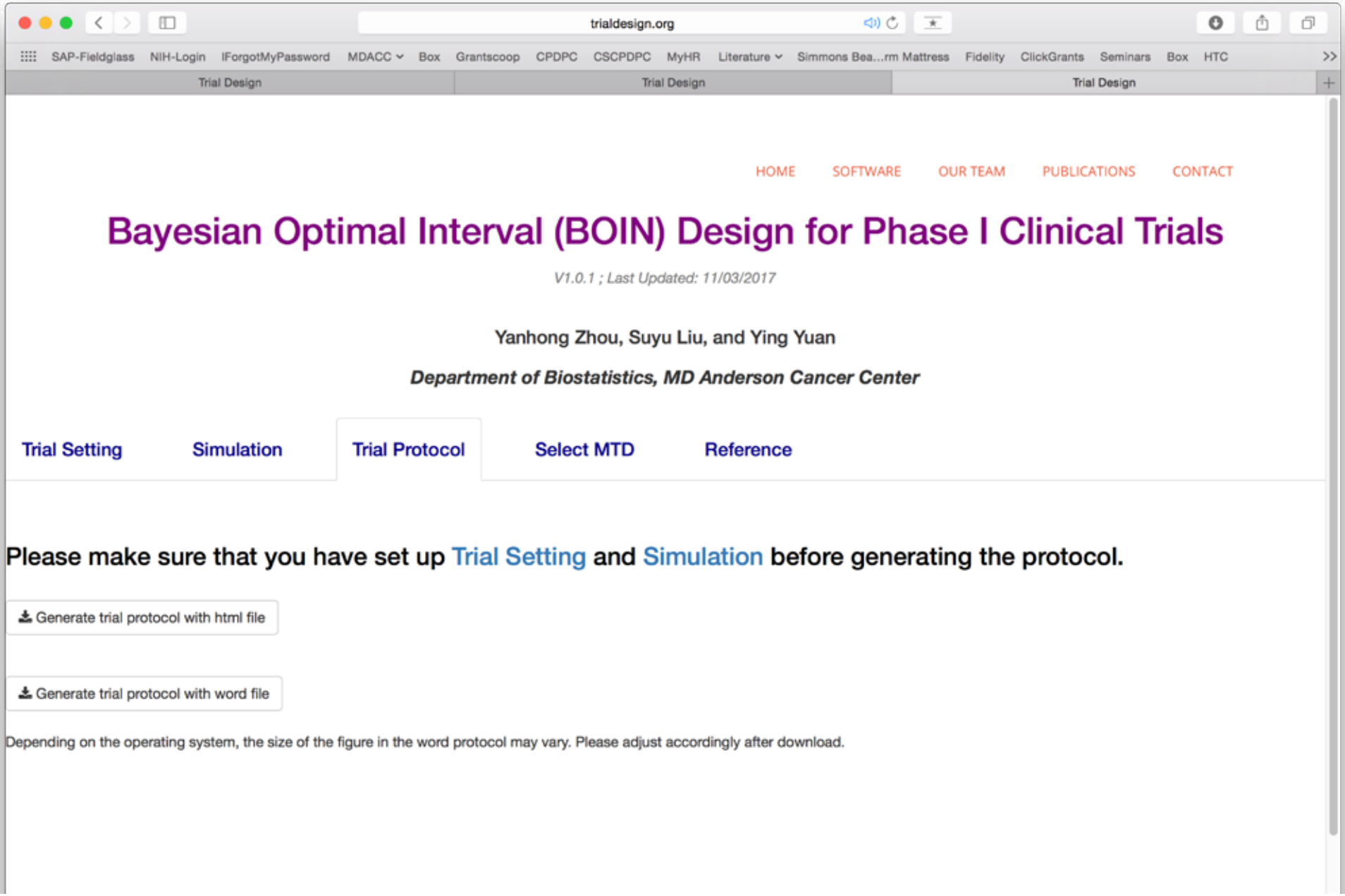
www.trialdesign.org



www.trialdesign.org



www.trialdesign.org



Key References

- Zhou H, Yuan Y and Nie L (2018) Accuracy, safety and reliability of novel Bayesian phase I trial designs. *Clinical Cancer Research*, 24, 4357-4364
- Liu S, Yuan Y (2015). Bayesian Optimal Interval Designs for Phase I Clinical Trials. *Journal of the Royal Statistical Society Series C*, 64(3), 507-523.
- Yuan Y, Hess K, Hilsenbeck S, Gilbert M(2016). Bayesian Optimal Interval Design: A Simple and Well-performing Design for Phase I Oncology Trials." *Clinical Cancer Research*, 22, 4291-4301.
- Lin R, Yin G (2017). Bayesian Optimal Interval Design for Dose Finding in Drug-Combination Trials." *Statistical Methods in Medical Research*, 26, 2155-2167.
- 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(20):4921-4930.
- Zhou H, Murray T, Pan, H and Yuan Y (2018) Comparative review of novel model-assisted designs for phase I clinical trials. *Statistics in Medicine*, 37, 2208-2222.

Thank you !