Model-assisted design for drug combination dose-finding trials

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Drug Combination

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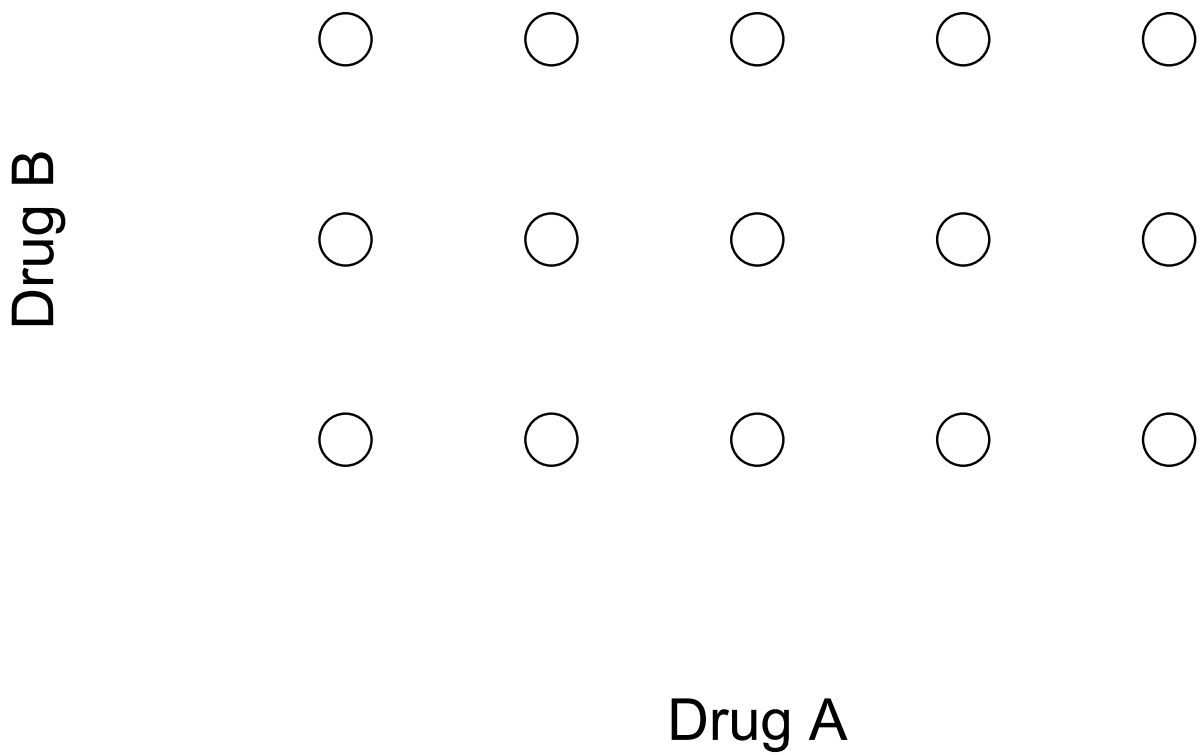
Synergistic treatment effect!

Challenges of drug combination trials

- Larger searching space $\Longrightarrow$ larger sample size required!
- Doses are only partially ordered in toxicity due to complicated drug-drug interaction



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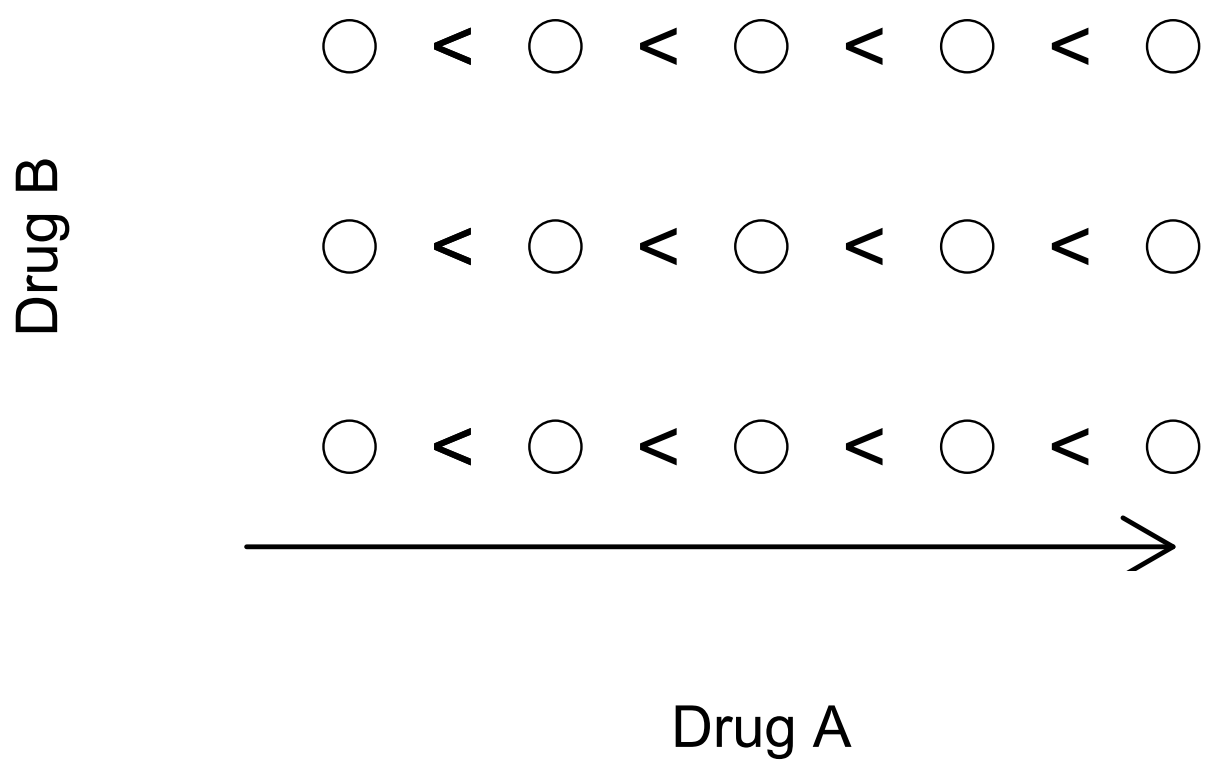

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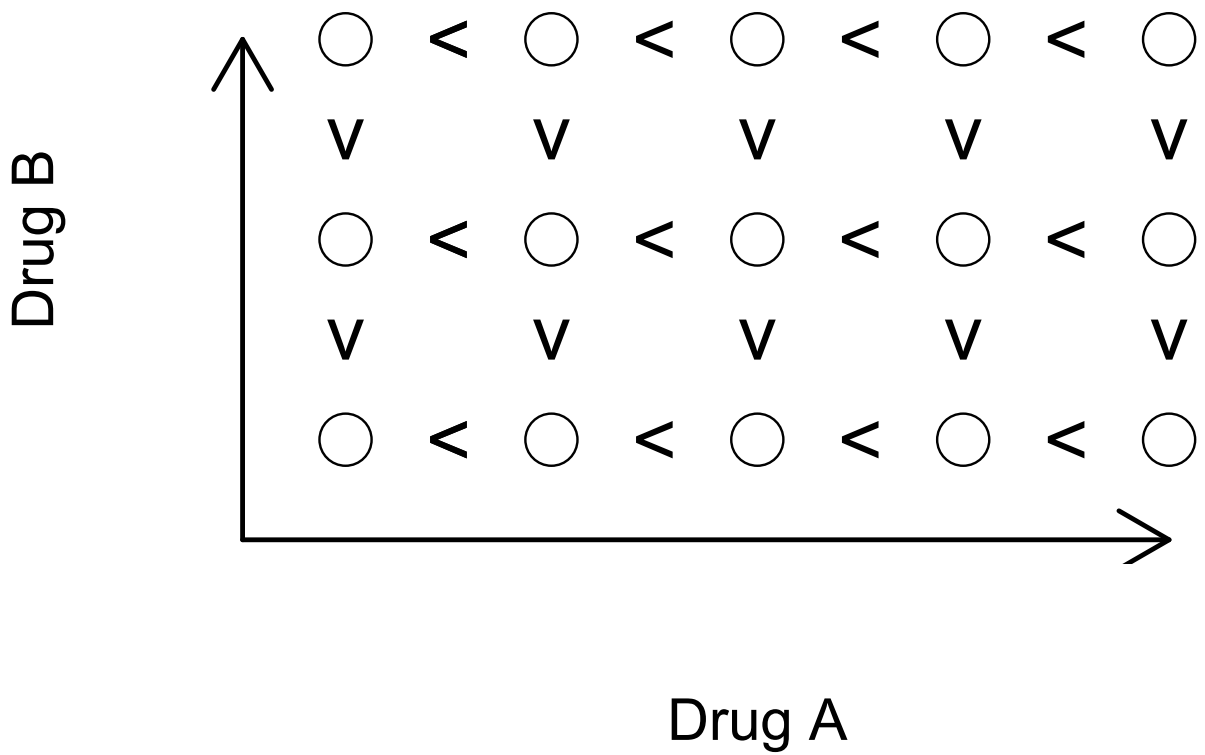

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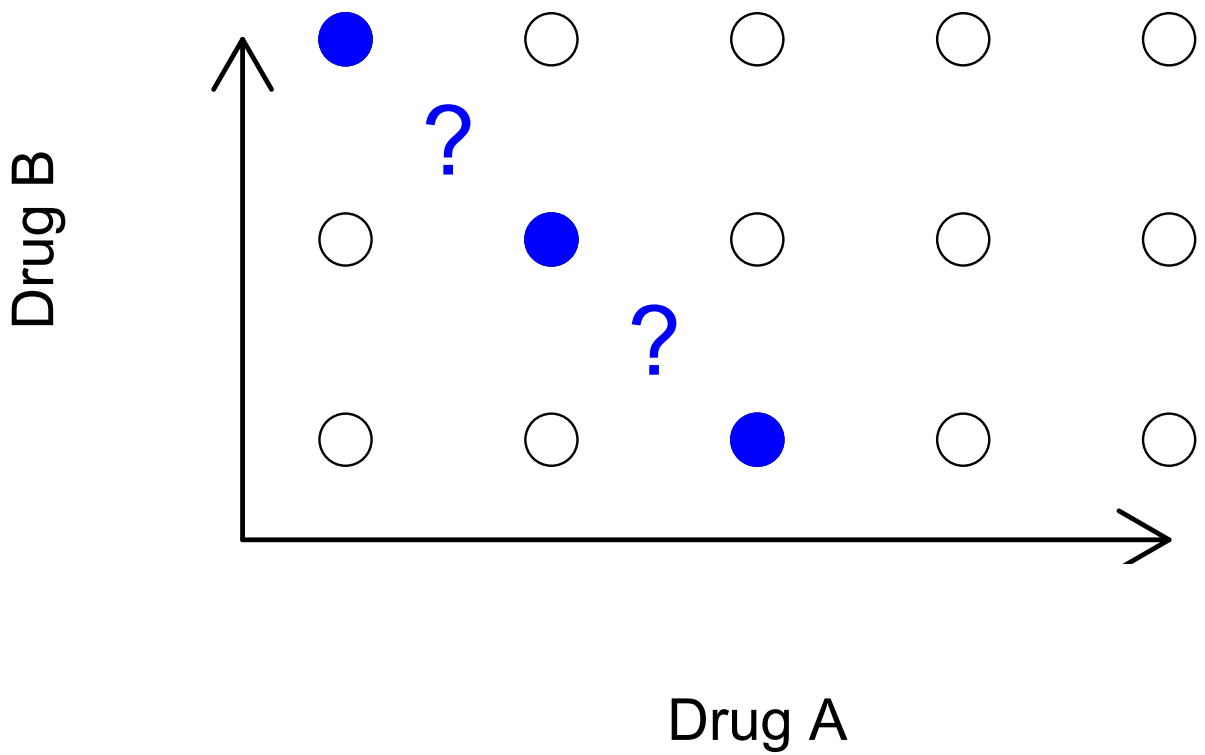
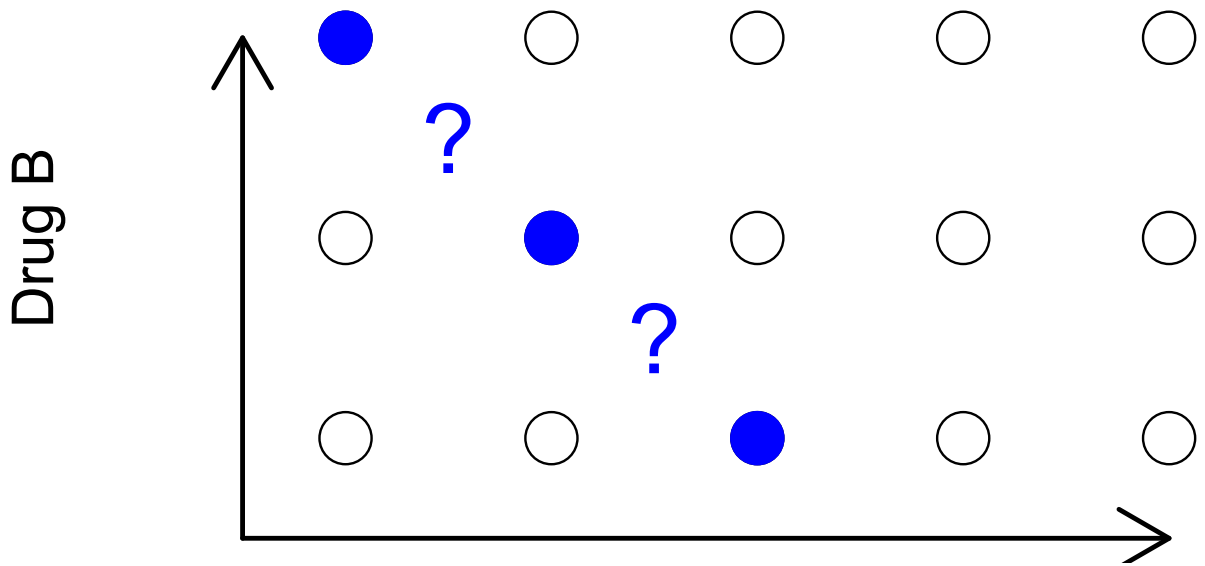


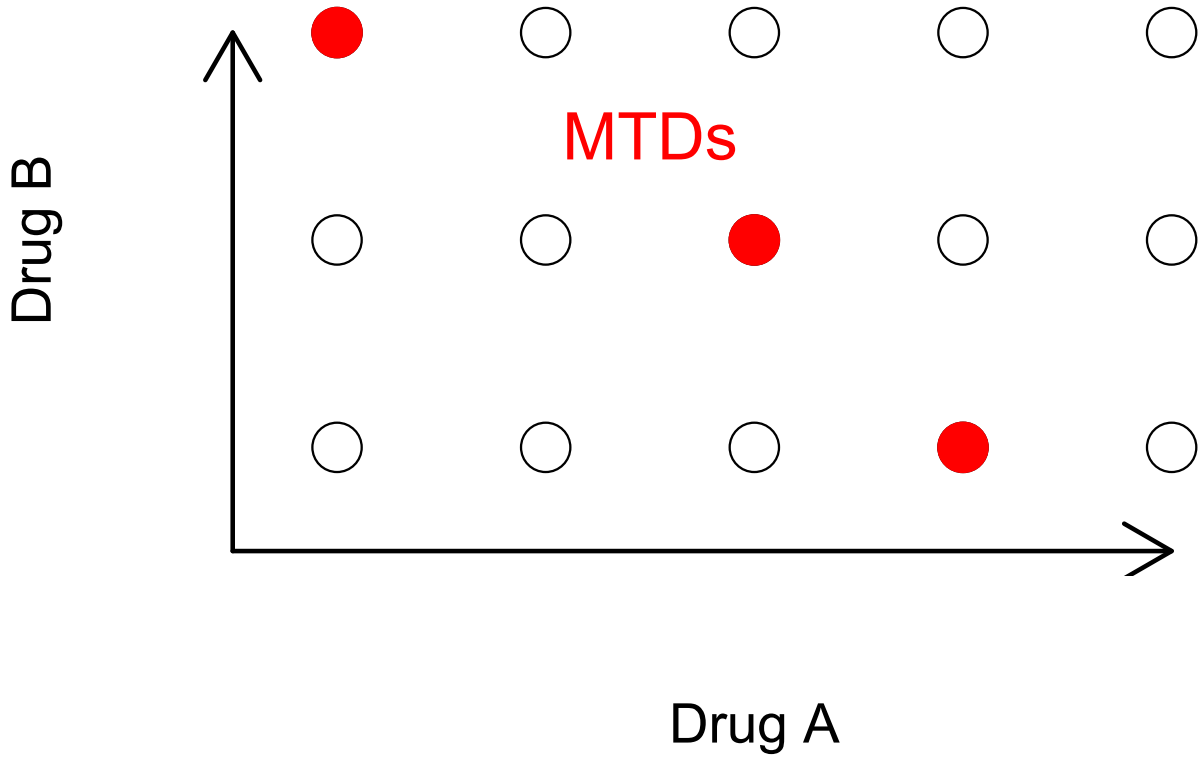
Challenges of drug combination trials

- Larger searching space $\Longrightarrow$ larger sample size required!
- Doses are only partially ordered in toxicity due to complicated drug-drug interaction $\Longrightarrow$ single-agent dose-finding methods cannot be directly used for combination trials.

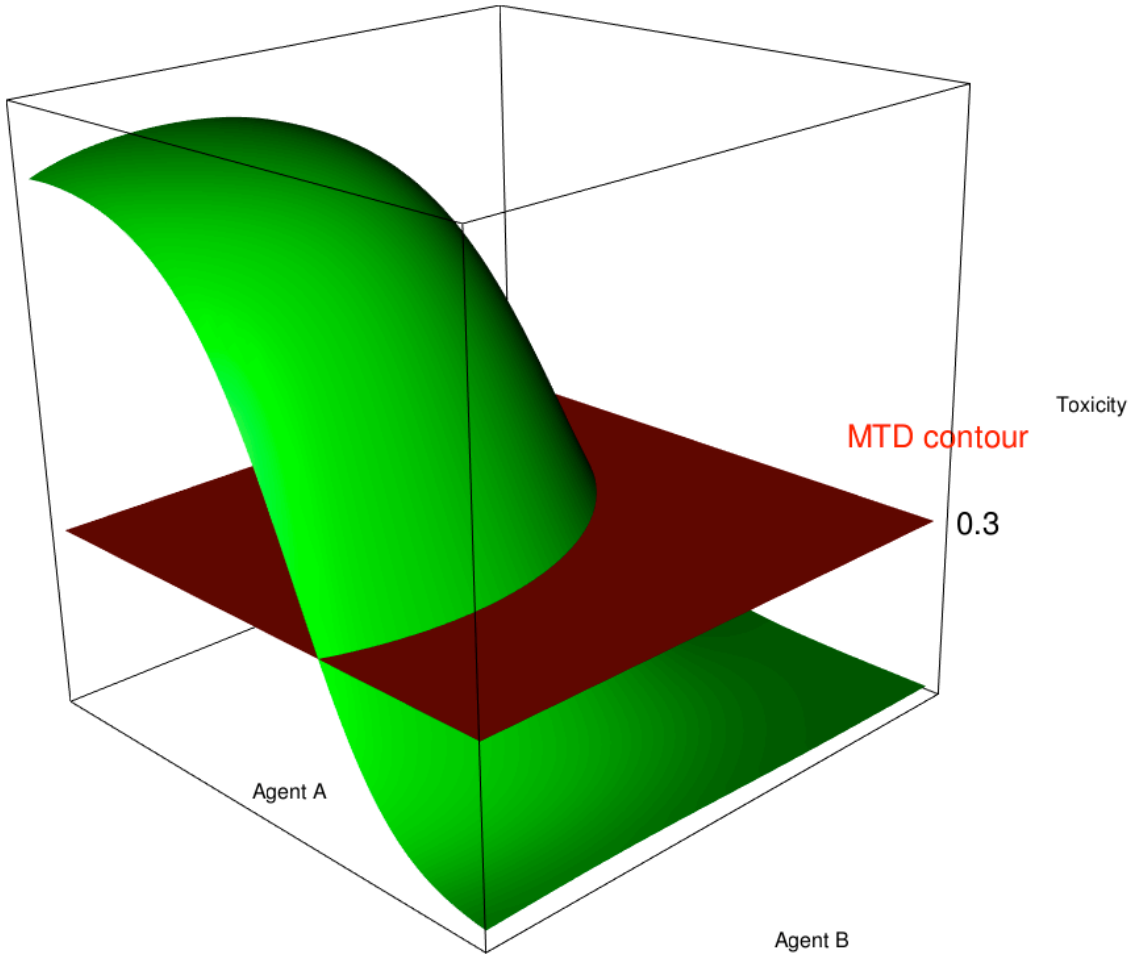


Challenges of drug combination trials

- Multiple MTDs may exist!



MTD contour



A key design question

- A fundamental question when designing a combination trial:

  Are we interested in finding **one MTD or the MTD contour (multiple MTDs)?**

- The answer to this question determines the choice of different design strategies.
- This important issue, unfortunately, is largely overlooked in practice.
- We here focus on finding a MTD, refer to Yuan and Zhang (2017) for designs to find the MTD contour.

Three types of design

- Algorithm-based designs
  - Dose transition is based on a set of prespecified rules/algorithm, e.g., 3+3 design or A+B design
  - Transparent, easy to implement, but perform poorly

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- **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/deescalation can be pretabulated before the onset of the trial in a fashion similar to the algorithm-based design (Yan, Mandrekar and Yuan, 2017)
  - Transparent, easy to implement and good performance
  - Examples: mtpi (Ji et al., 2007), BOIN (Liu and Yuan, 2015), and keyboard design (Yan, Mandrekar and Yuan, 2017).

Finding a single MTD

- Many novel model-based combination designs have been proposed to find a single MTD (Thall, et al, 2003; Yin and Yuan 2009a, 2009b; Braun and Wang, 2010; Yuan and Yin, 2011; Wage et al., 2011; Riviere, et al., 2014, 2015; ...).
- These designs perform well in simulation, but are rarely used in practice.
  - Statistically and computationally complicated
  - Lack of easy-to-use software
  - Model-based, thus robustness can be a potential issue because of complicated two-dimensional dose searching space. In addition, incoherent dose escalation could be rampant
- Riviere et al. (2014) reviewed 162 drug-combination phase I trials published 2011-2013, among which 88% used the 3+3 design.

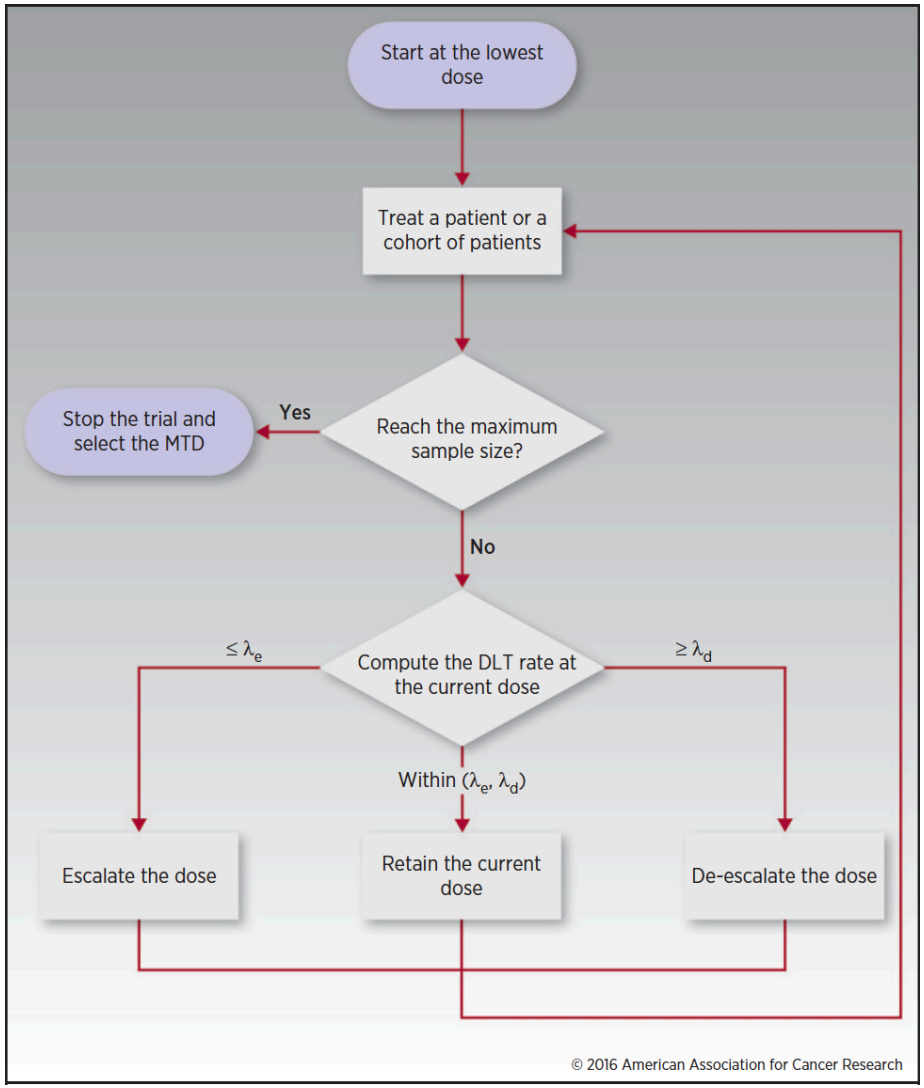
Coherent design

- A design is coherent if it will never escalate the dose when the latest treated patient experiences toxicity; and will never deescalate the dose when the latest treated patient does not experience toxicity (Cheung, 2005).
- A design is long-memory coherent if it will never escalate the dose when the observed toxicity rate at the current dose is higher than the target toxicity rate; and will never deescalate the dose when the observed toxicity rate at the current dose is lower than the target toxicity rate (Liu and Yuan, 2015).
- Long-memory coherent is a natural requirement in practice.

BOIN drug-combination design

- The Bayesian optimal interval (BOIN) drug-combination design (Lin and Yin, 2016; Yuan and Zhang, 2017) is a model-assisted design that is as transparent as the 3+3 design, but yields substantially better performance.
- The BOIN drug-combination design is long-memory coherent, which may not be true for most existing model-based drug-combination designs.
- The BOIN drug-combination design is an extension of the BOIN single-agent design (Liu and Yuan, 2015), and makes the decision of dose escalation/de-escalation based on the same rule as the latter.

Bayesian optimal interval (BOIN) design



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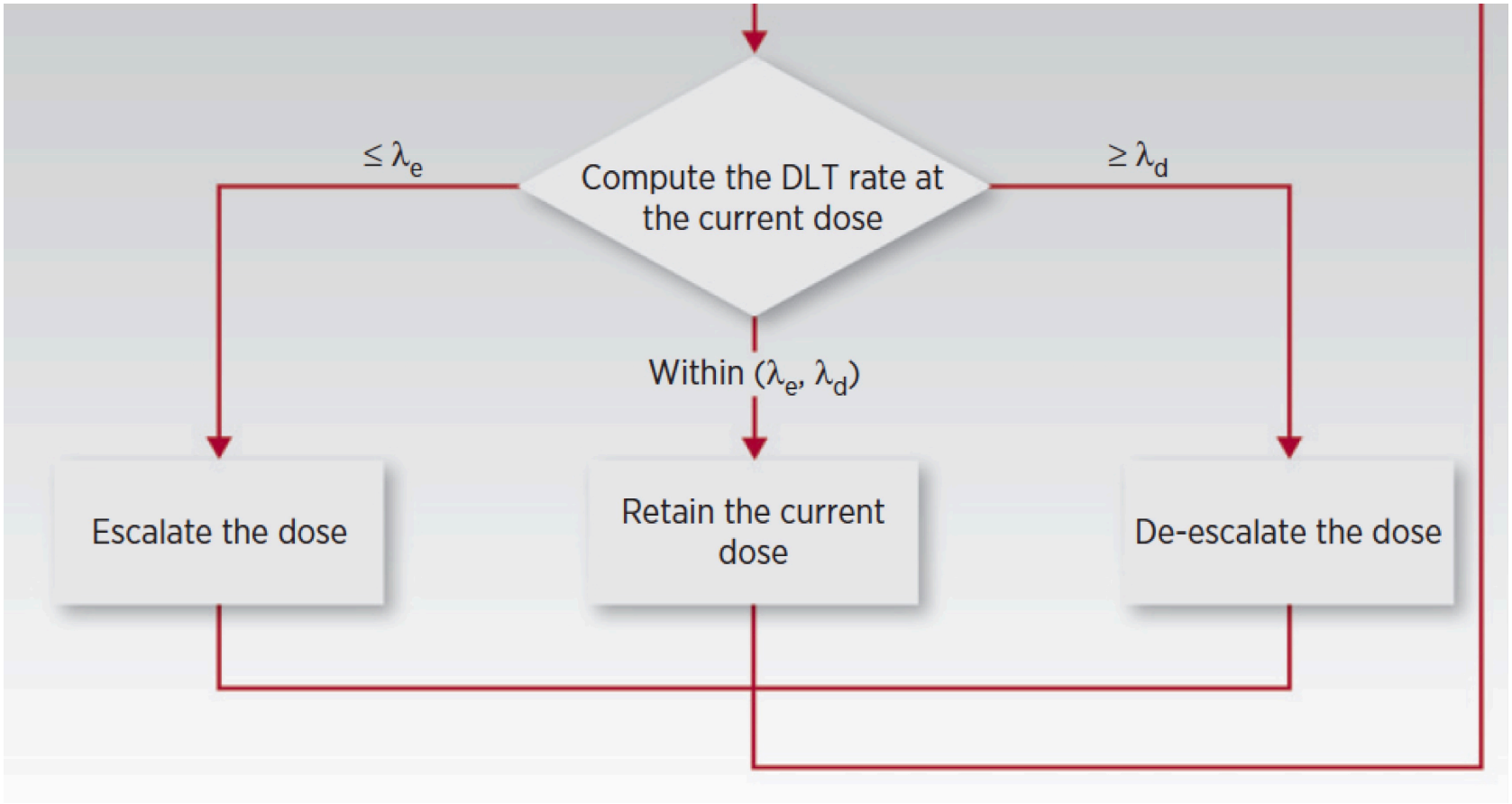
BOIN dose escalation/deescalation rule



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Escalation/de-escalation boundaries

Table: The escalation/de-escalation boundaries (λ_e, λ_d) under the BOIN design for different target toxicity rates*.

boundaries	Target toxicity rate ϕ					
	0.15	0.2	0.25	0.3	0.35	0.4
λ_e	0.118	0.157	0.197	0.236	0.276	0.316
λ_d	0.179	0.238	0.298	0.358	0.419	0.479

* using the default underdosing toxicity rate $\phi_1 = 0.6\phi$ and overdosing toxicity rate $\phi_2 = 1.4\phi$.

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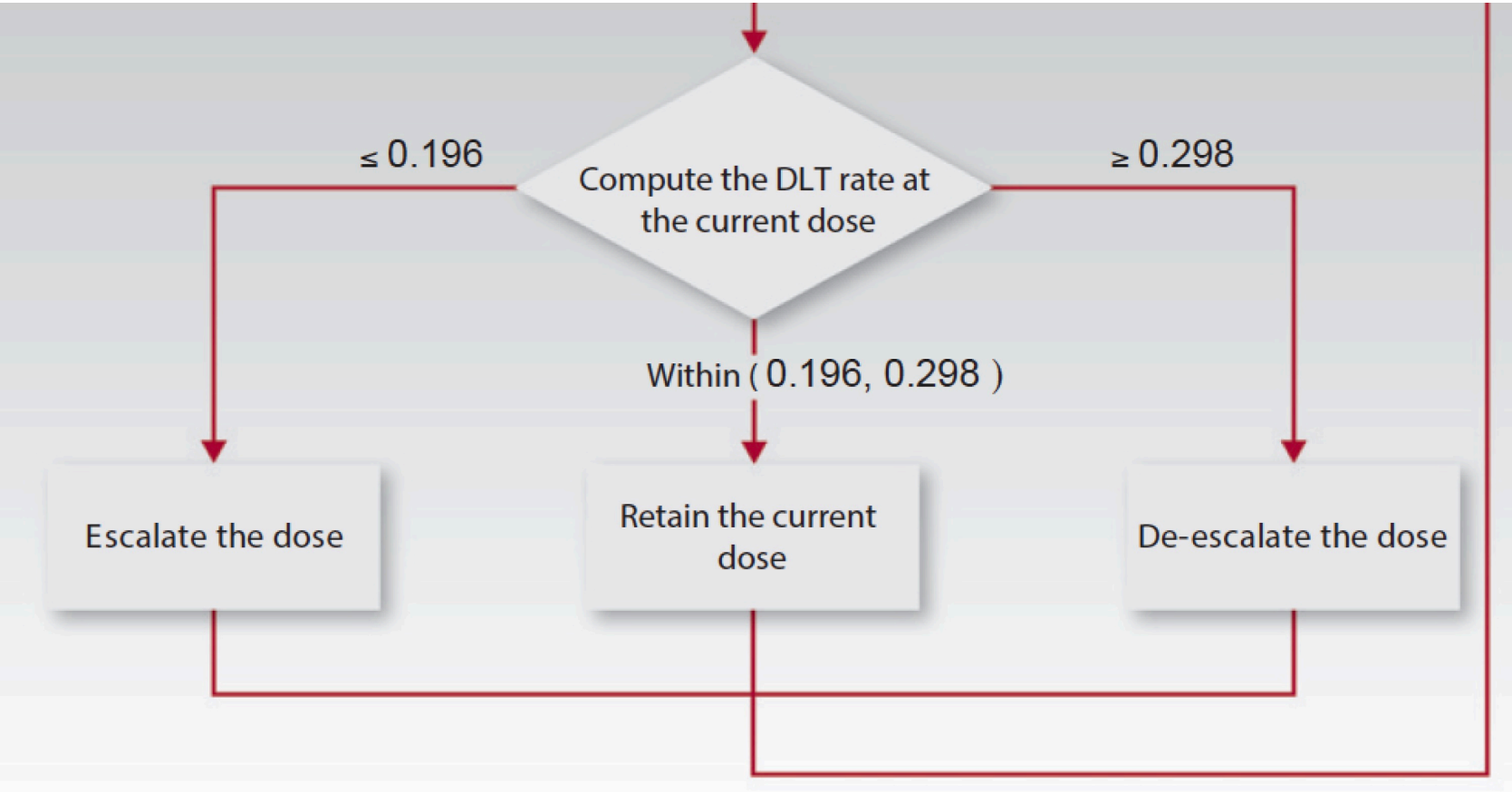
BOIN design with target toxicity rate of 25%



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Statistical principle behind BOIN design

- The BOIN is obtained by minimizing the decision error for dose escalation/deescalation within the whole class of nonparametric designs that do not assume a parametric dose-response curve

A class of nonparametric designs

1. The first cohort are treated at the lowest dose level.
2. At the current dose level j:
   - if $\hat{\pi}_{T,j} \leq \lambda_{1j}$, escalate
   - if $\hat{\pi}_{T,j} \geq \lambda_{2j}$, deescalate
   - otherwise, i.e., $\lambda_{1j} < \hat{\pi}_{T,j} < \lambda_{2j}$, retain

   where $\lambda_{1j} \equiv \lambda_{1j}(n_j, \phi)$ and $\lambda_{2j} \equiv \lambda_{2j}(n_j, \phi)$ denote the dose escalation and deescalation boundaries.
3. Repeat step 2 until the maximum sample size is reached.

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3. Repeat step 2 until the maximum sample size is reached.

Because λ_{1j} and λ_{2j} can freely vary across the dose levels (i.e., j) and the number of patients treated (i.e., n_j), this class of designs include ALL possible nonparametric designs that do not impose a dose-toxicity curve.

Notations and setup

- Specify three point hypotheses

$$\begin{aligned} H_0 : &\quad p_j = \phi \\ H_1 : &\quad p_j = \phi_1 \\ H_2 : &\quad p_j = \phi_2, \end{aligned}$$

- ϕ_1 is the highest toxicity probability that is deemed subtherapeutic (i.e., below the MTD) such that dose escalation should be made
- ϕ_2 is the lowest toxicity probability that is deemed overly toxic such that dose deescalation is required
- Example: $\phi = 0.3$, $\phi_1 = 0.2$ and $\phi_2 = 0.4$

Remarks on the 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 toxicity 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 the 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 6% power to distinguish 0.35 from 0.25 with 30 patients.
- As default values, we recommend $\phi_1 = 0.6\phi$ and $\phi_2 = 1.4\phi$.
  - e.g., when $\phi = 0.25$, $\phi_1 = 0.15$ and $\phi_2 = 0.35$.

Correct and incorrect decisions

- The correct decisions under H_0, H_1 and H_2 are $\mathcal{R}$, $\mathcal{E}$ and $\mathcal{D}$, respectively, where $\mathcal{R}$, $\mathcal{E}$ and $\mathcal{D}$ denote dose retainment (of the current dose level), escalation and deescalation.
- The incorrect decisions under H_0, H_1 and H_2 are $\bar{\mathcal{R}}$, $\bar{\mathcal{E}}$ and $\bar{\mathcal{D}}$, where $\bar{\mathcal{R}}$ denotes the decisions complementary to $\mathcal{R}$ (i.e., $\bar{\mathcal{R}}$ includes $\mathcal{E}$ and $\mathcal{D}$), and $\bar{\mathcal{D}}$ and $\bar{\mathcal{R}}$ are defined similarly.

Decision error rate

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

$$\begin{aligned}\alpha &\equiv \text{pr}(\text{incorrect decision on dosing}) \\ &= \text{pr}(H_0)\text{pr}(\bar{\mathcal{R}}|H_0) + \text{pr}(H_1)\text{pr}(\bar{\mathcal{E}}|H_1) + \text{pr}(H_2)\text{pr}(\bar{\mathcal{D}}|H_2)\end{aligned}$$

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&= \text{pr}(H_0)\{Bin(n_j\lambda_{1j}; n_j, \phi) + 1 - Bin(n_j\lambda_{2j} - 1; n_j, \phi)\} \\
&\quad + \text{pr}(H_1)\{1 - Bin(n_j\lambda_{1j}; n_j, \phi_1)\} \\
&\quad + \text{pr}(H_2)Bin(n_j\lambda_{2j} - 1; n_j, \phi_2)
\end{aligned}
$$

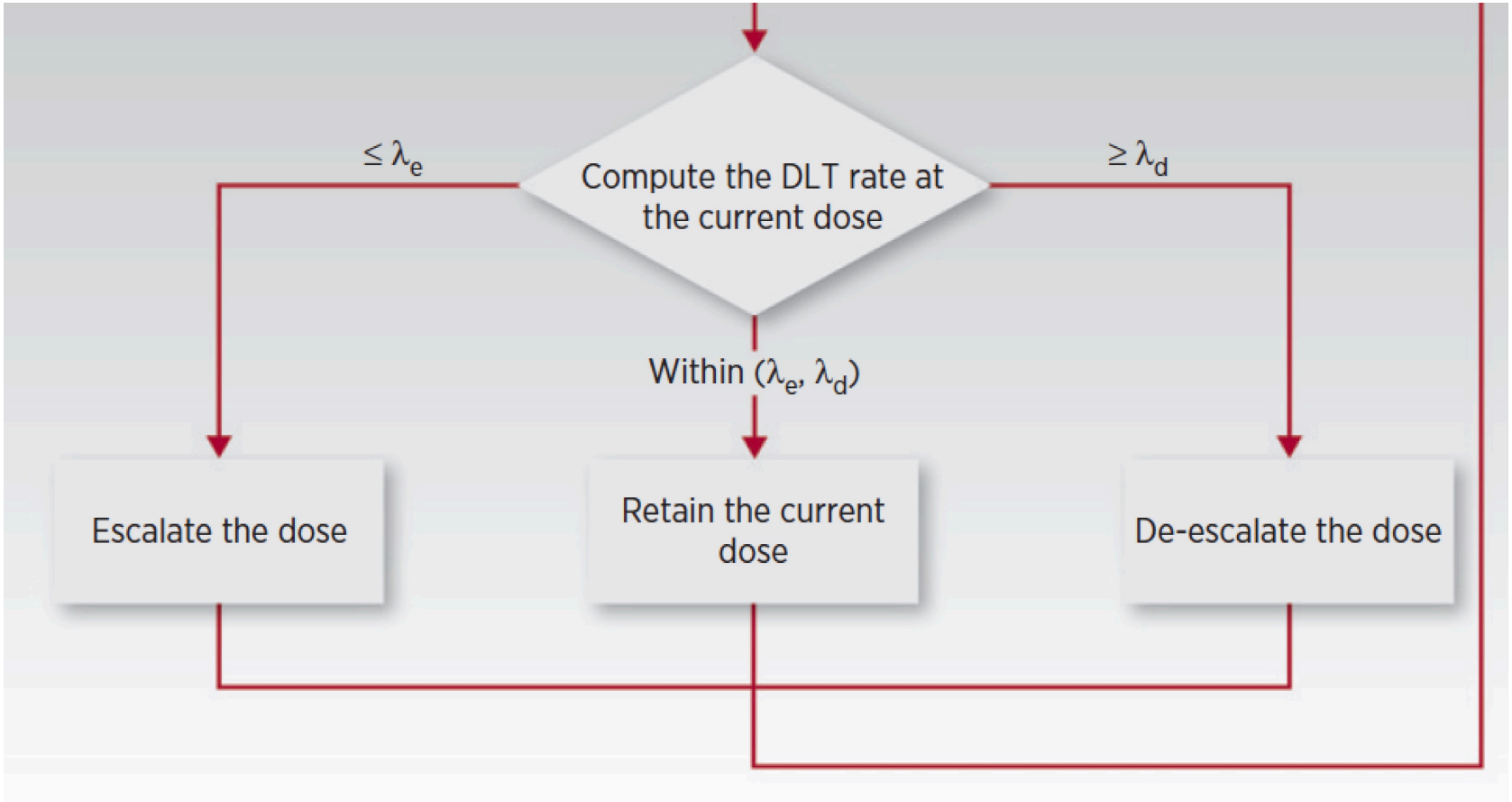
Optimal escalation/deescalation boundaries

- Assuming the non-informative prior that the current dose has the equal probability of being at, above or below the MTD, the optimal dose escalation/deescalation boundaries that minimize incorrect dose assignment are given by

$$\lambda_{1j} = \log\left(\frac{1-\phi_1}{1-\phi}\right) \Big/ \log\left(\frac{\phi(1-\phi_1)}{\phi_1(1-\phi)}\right)$$
$$\lambda_{2j} = \log\left(\frac{1-\phi}{1-\phi_2}\right) \Big/ \log\left(\frac{\phi_2(1-\phi)}{\phi(1-\phi_2)}\right).$$

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

Dose escalation using the BOIN design



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Statistical properties of the BOIN

Coherence

The BOIN design is (long-memory) coherent in the sense that the design will never escalate the dose when the observed toxicity rate $\hat{p}_j$ at the current dose is higher than the target toxicity rate ϕ; and will never deescalate the dose when the observed toxicity rate $\hat{p}_j$ at the current dose is lower than the target toxicity rate ϕ

- Example: suppose target toxicity rate = 30%, if 1/3 has toxicity, the BOIN design will never escalate dose; if 0/3 has toxicity, the design will never deescalate dose.

Consistence

Under the BOIN design, dose allocation and selection converge to the target dose.

BOIN drug-combination design

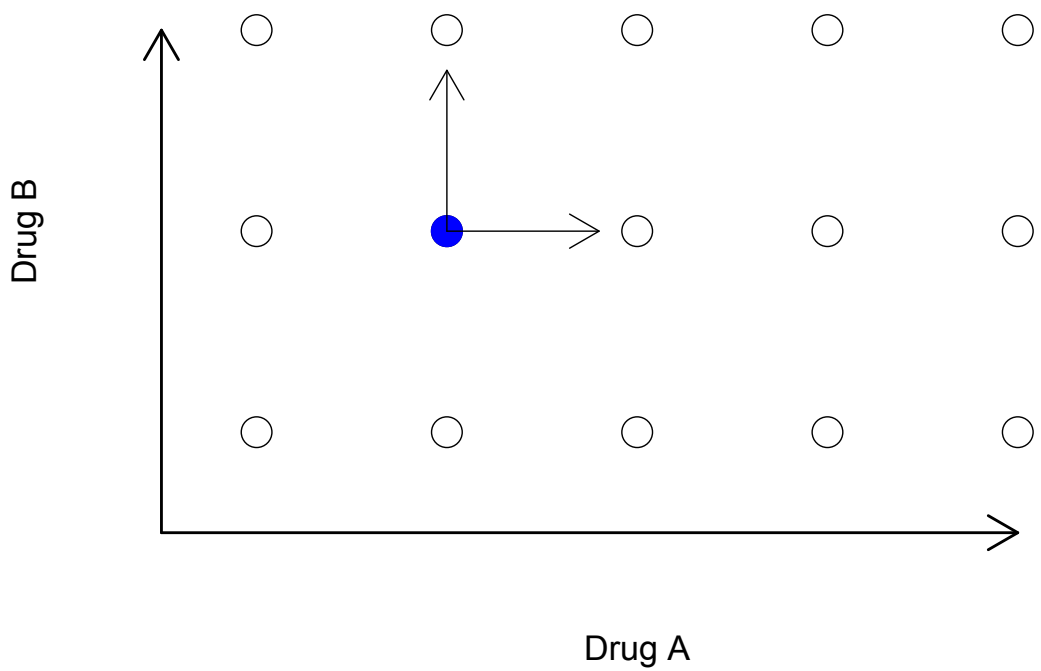
- The BOIN drug-combination design uses the same escalation/de-escalation rule as the BOIN single-agent design
- Thus, the BOIN drug-combination design is coherent, consistent and easy to implement in practice.
- The only difference is that, in combination trials, when we decide to escalate or de-escalate the dose, there are more than one neighbor doses that we can move to.

BOIN drug-combination design

- Let A_jB_k denote the combination of dose level j of agent A with dose level k of agent B.
- Let p_{jk} denote the toxicity rate of A_jB_k.
- The BOIN drug-combination design makes its choice based on $\Pr(p_{jk} \in (\lambda_e, \lambda_d)|\text{data})$, which measures how likely the combination has acceptable toxicity given the observed data.

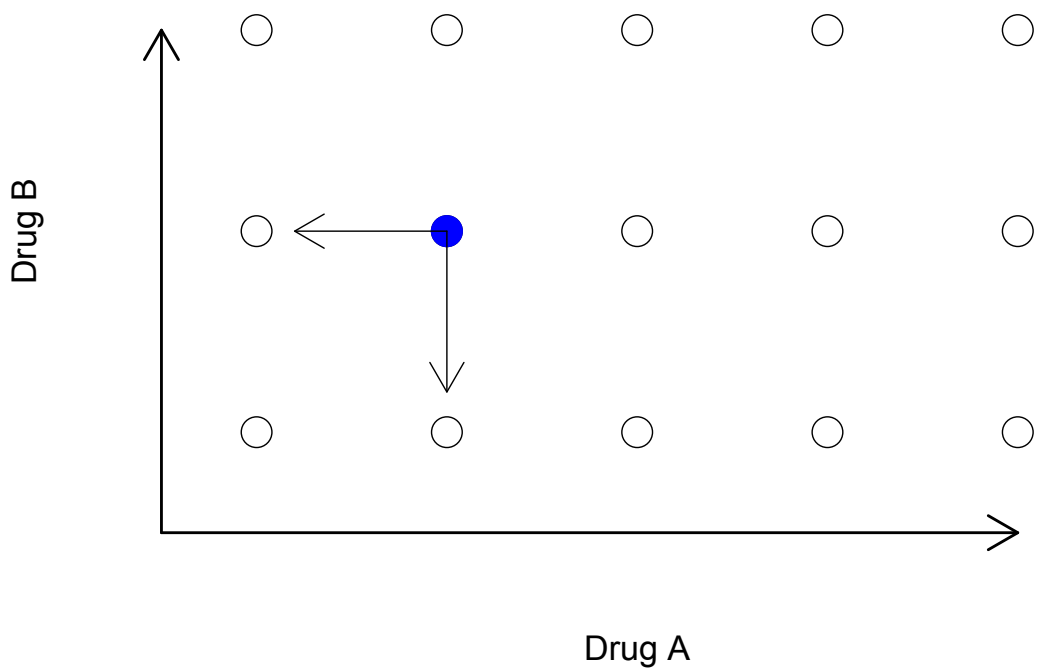
Dose escalation

- When the BOIN rule says escalation, we escalate the dose to $A_{j+1}B_k$ or A_jB_{k+1}, the one that has the largest value of $Pr(p_{j'k'} \in (\lambda_e, \lambda_d)|n_{j'k'}, y_{j'k'})$, where $(j', k') = (j + 1, k)$ or $(j, k + 1)$.



Dose de-escalation

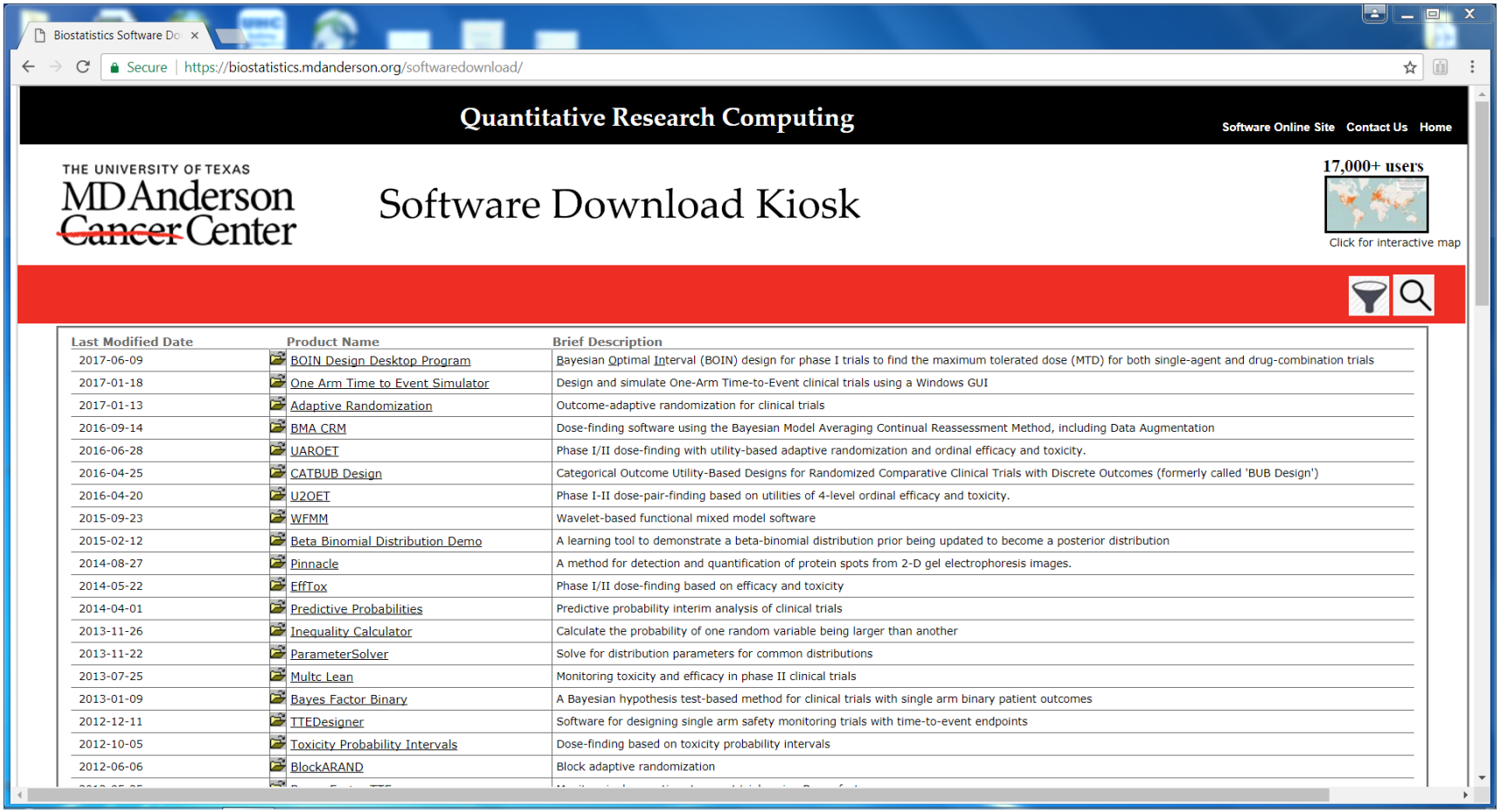
- When the BOIN rule says de-escalation, we de-escalate the dose to $A_{j-1}B_k$ or A_jB_{k-1}, the one that has the largest value of $Pr(p_{j'k'} \in (\lambda_e, \lambda_d)|n_{j'k'}, y_{j'k'})$, where $(j', k') = (j-1, k)$ or $(j, k-1)$.



Software

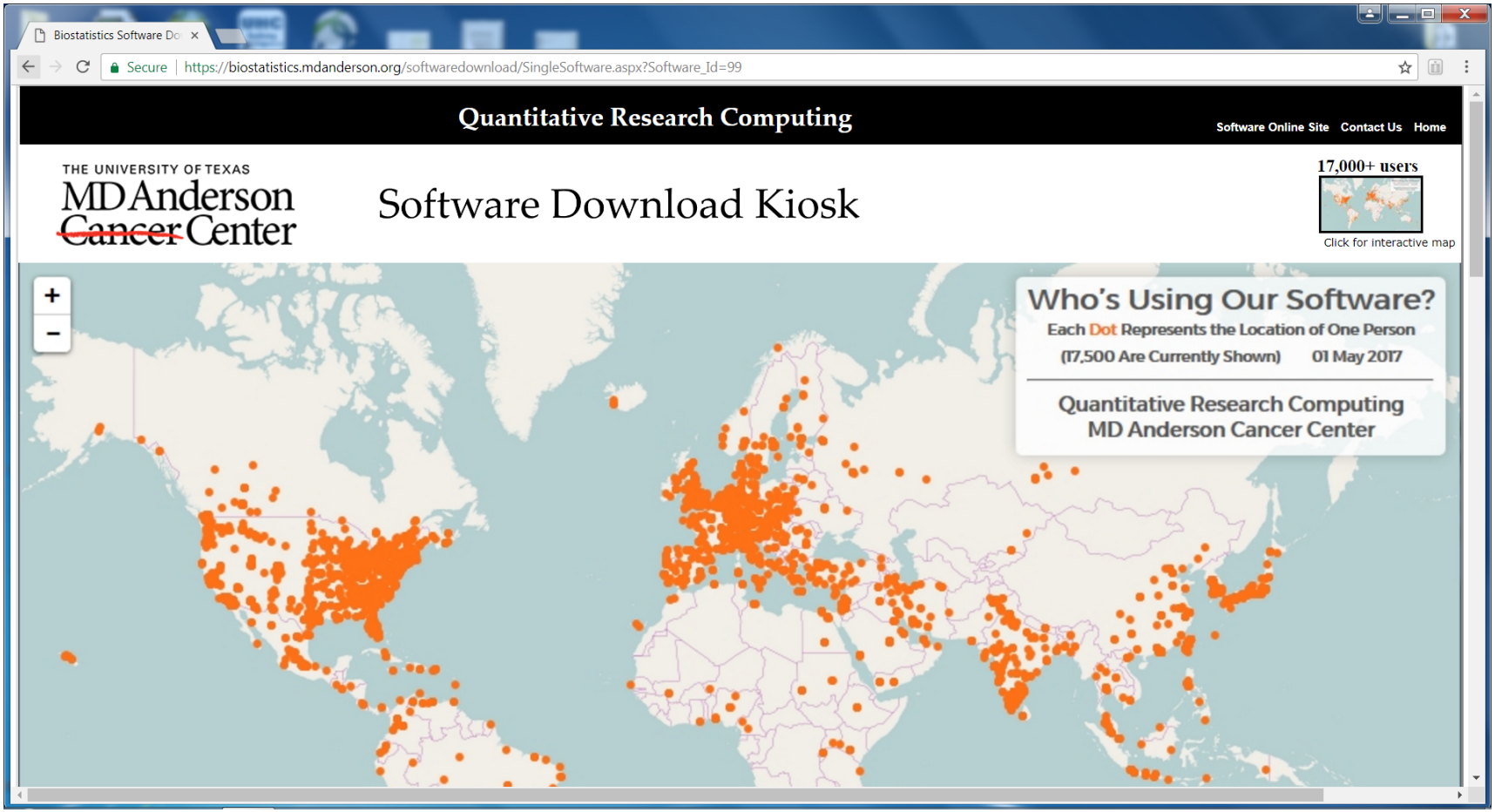
- Windows desktop program for implementing the BOIN combination design is freely available at MD Anderson Biostatistics software download website `https://biostatistics.mdanderson.org/softwaredownload/SingleSoftware.aspx?Software_Id=99`
- Online app at `http://www.trialdesign.org`
- R package "BOIN" available at CRAN

BOIN 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 I/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 I-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 I/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

BOIN Desktop Program



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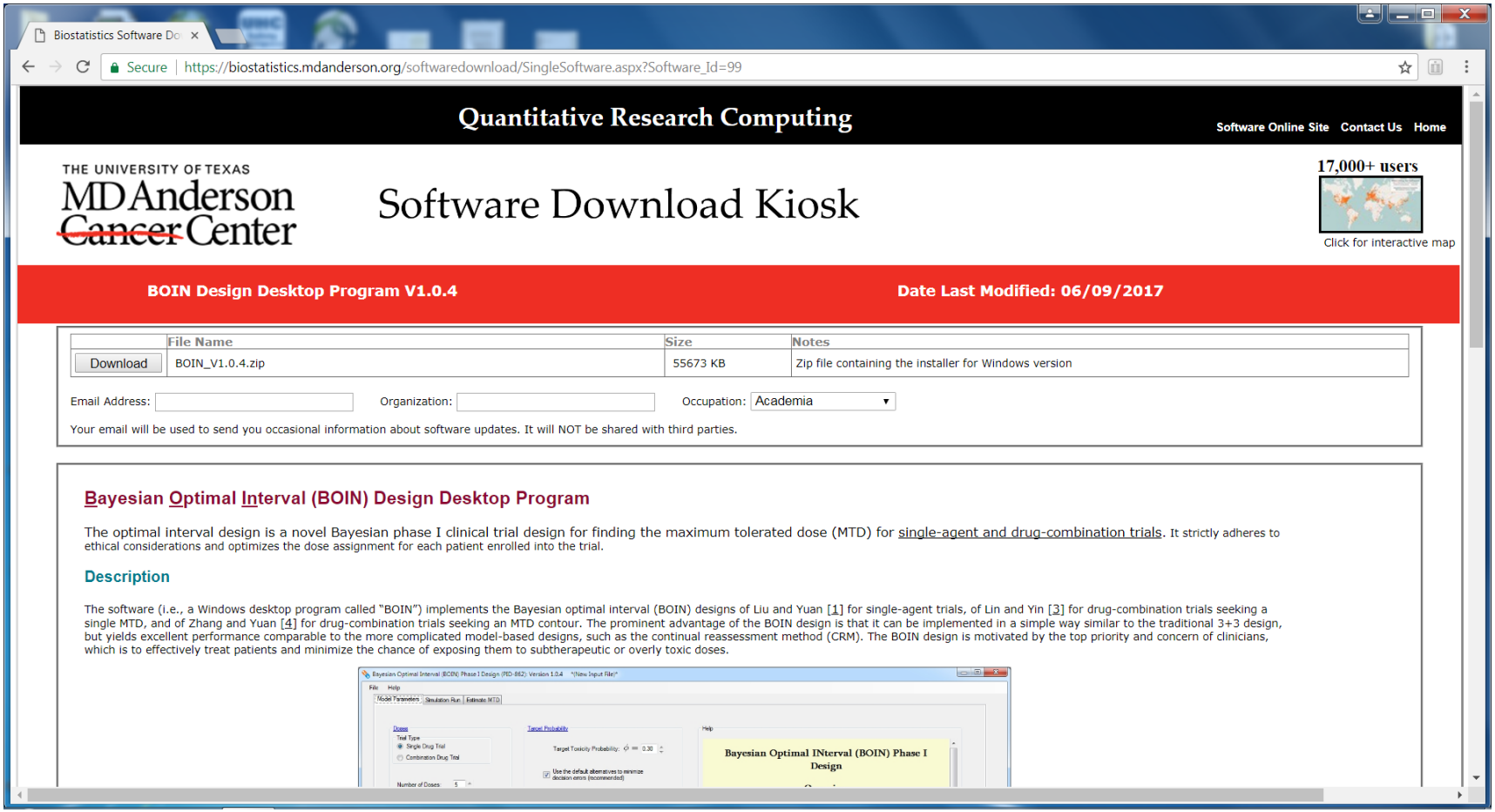

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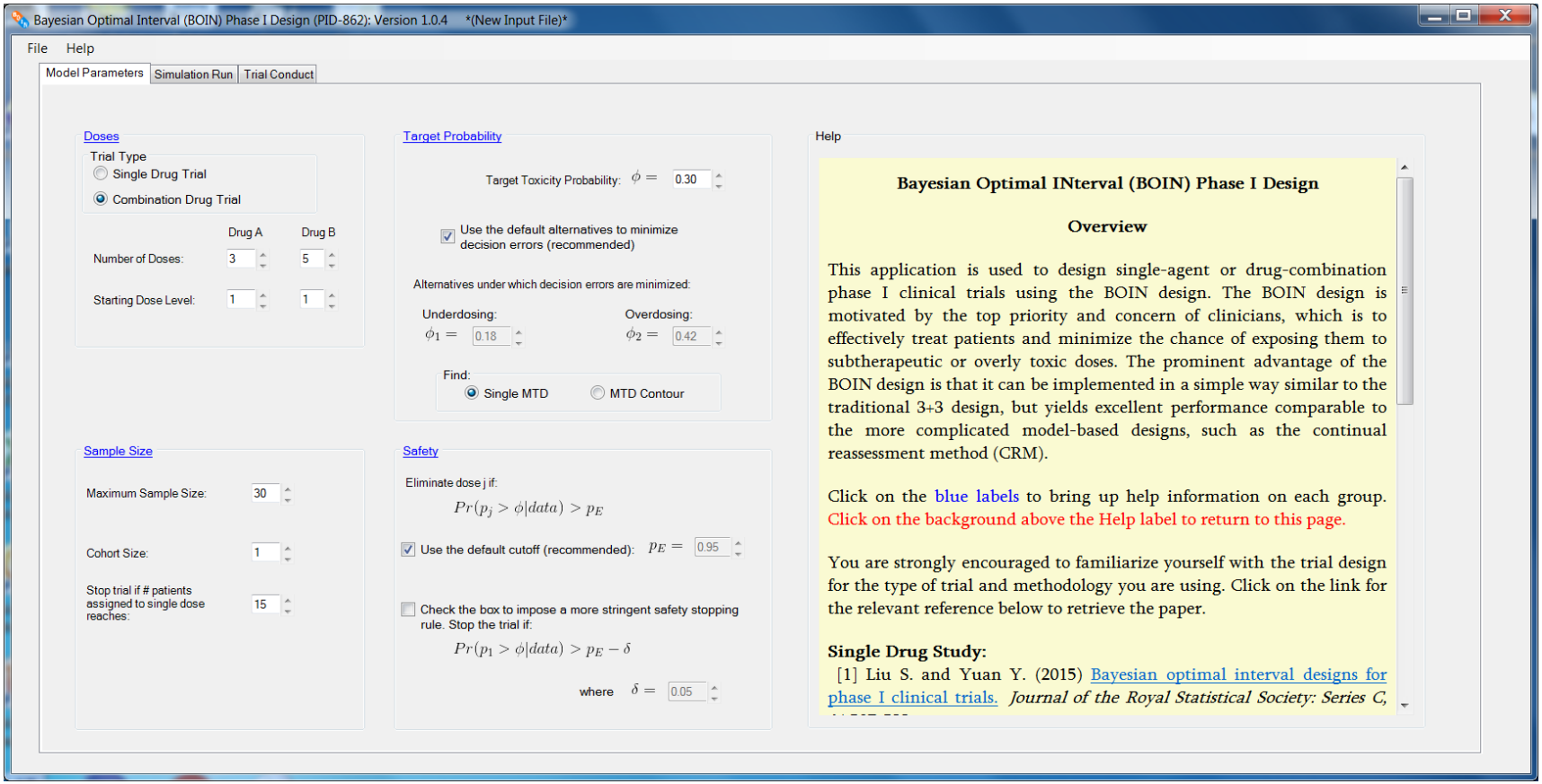

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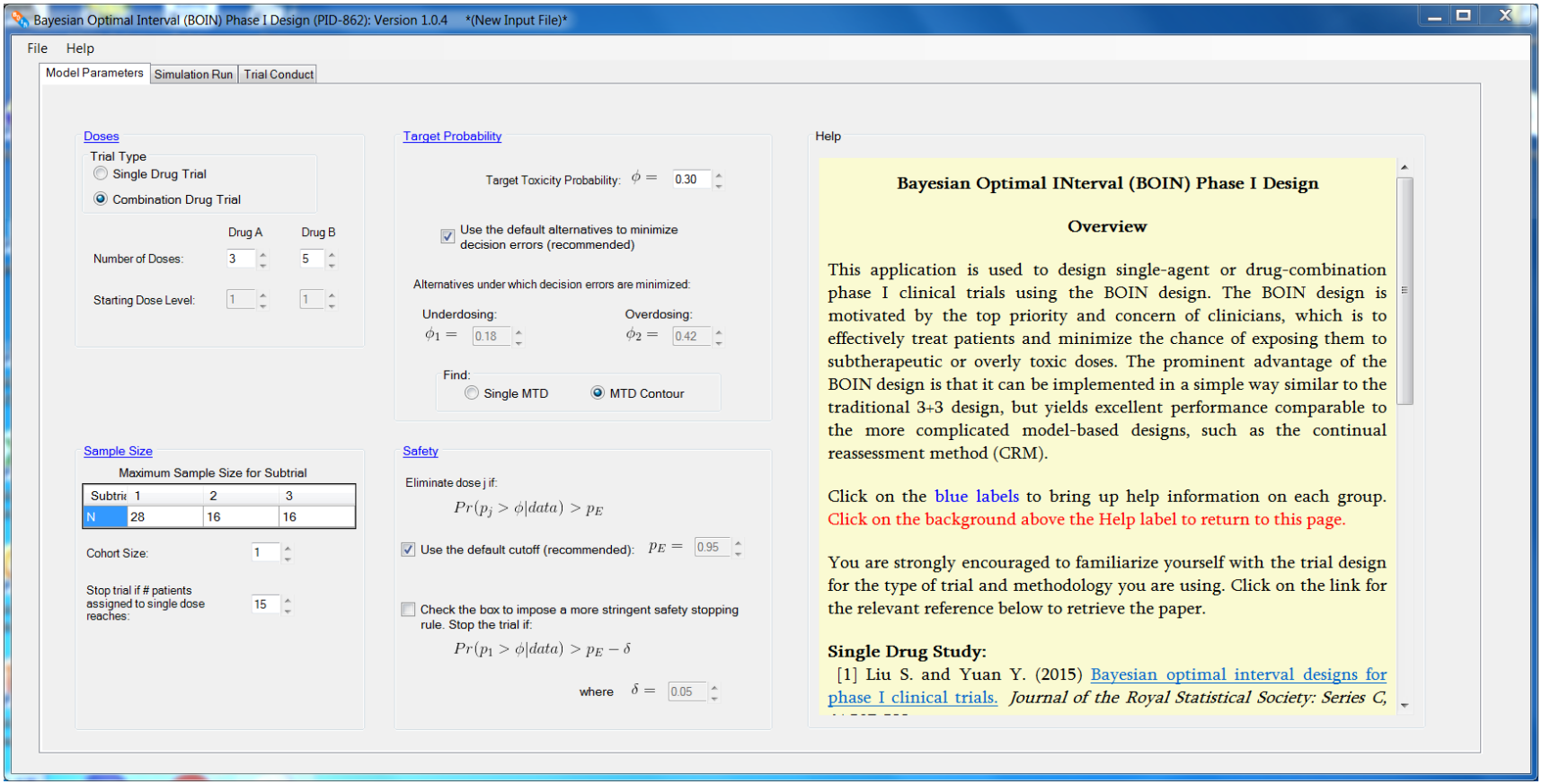

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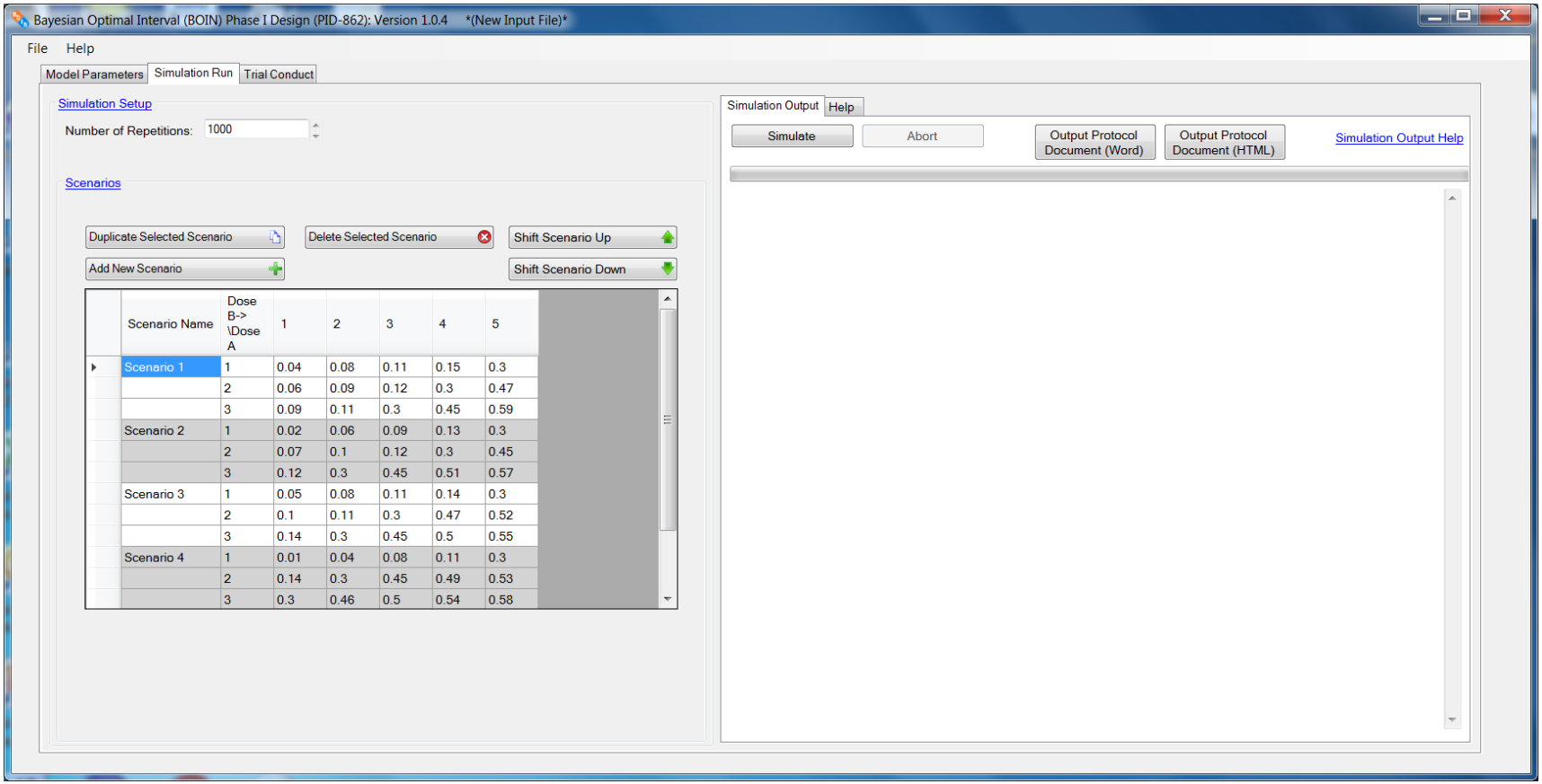

Scenario Name	Dose B-> \Dose A	1	2	3	4	5
Scenario 1	1	0.04	0.08	0.11	0.15	0.3
	2	0.06	0.09	0.12	0.3	0.47
	3	0.09	0.11	0.3	0.45	0.59
Scenario 2	1	0.02	0.06	0.09	0.13	0.3
	2	0.07	0.1	0.12	0.3	0.45
	3	0.12	0.3	0.45	0.51	0.57
Scenario 3	1	0.05	0.08	0.11	0.14	0.3
	2	0.1	0.11	0.3	0.47	0.52
	3	0.14	0.3	0.45	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

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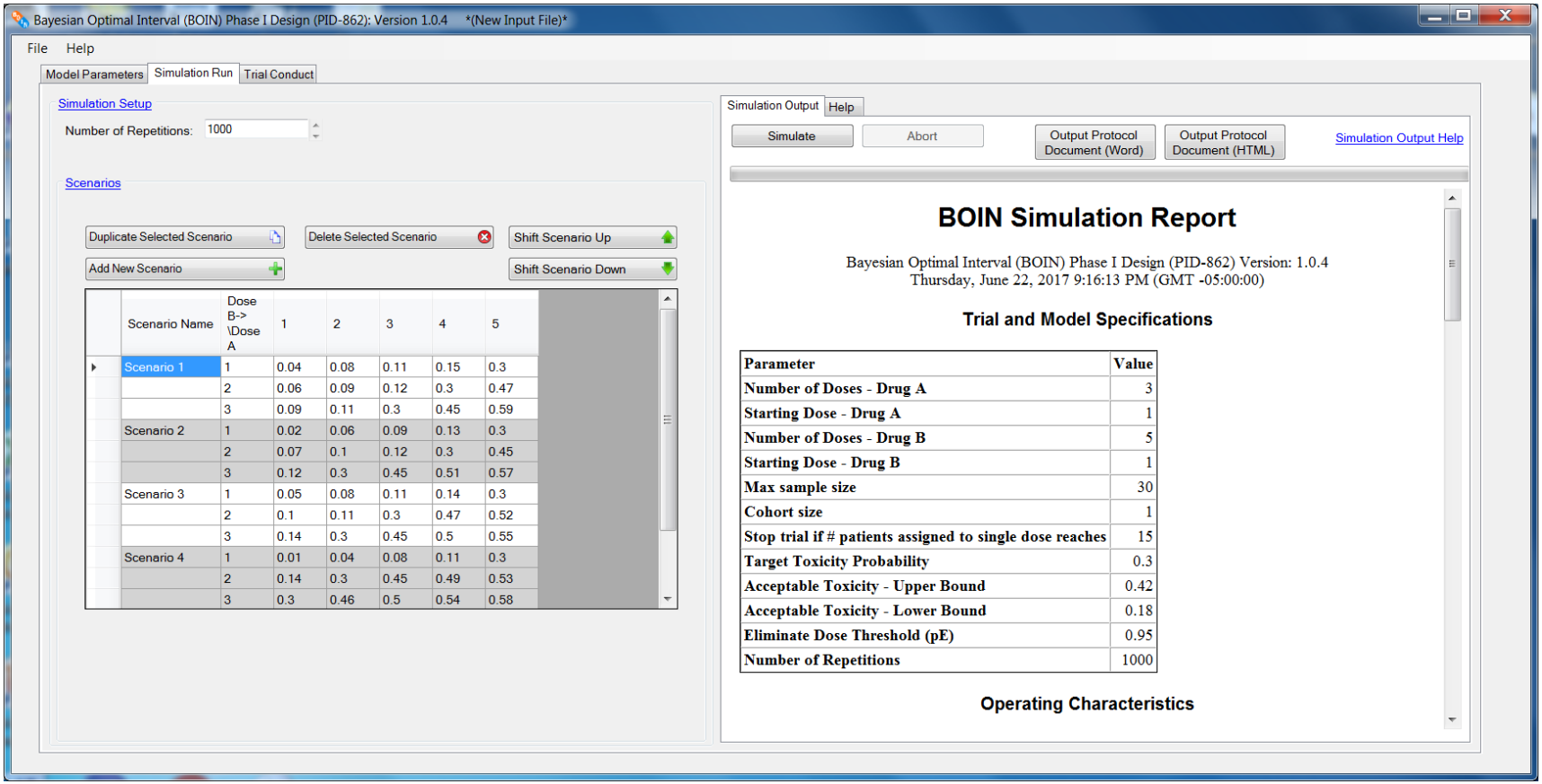

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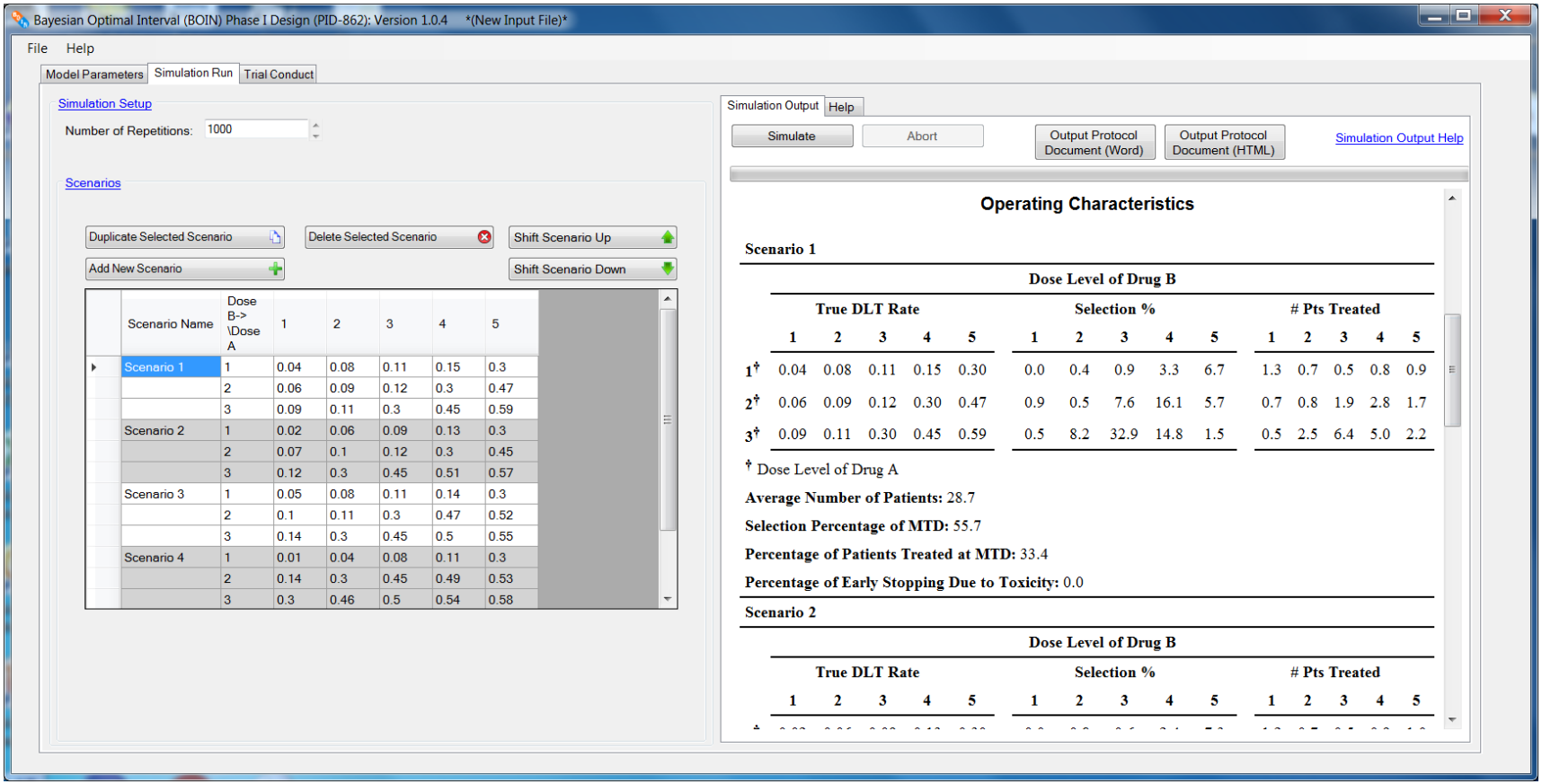
	3	0.14	0.3	0.45	0.5	0.55
Scenario 4	1	0.01	0.04	0.08	0.11	0.3
	2	0.14	0.3	0.45	0.49	0.53
	3	0.3	0.46	0.5	0.54	0.58

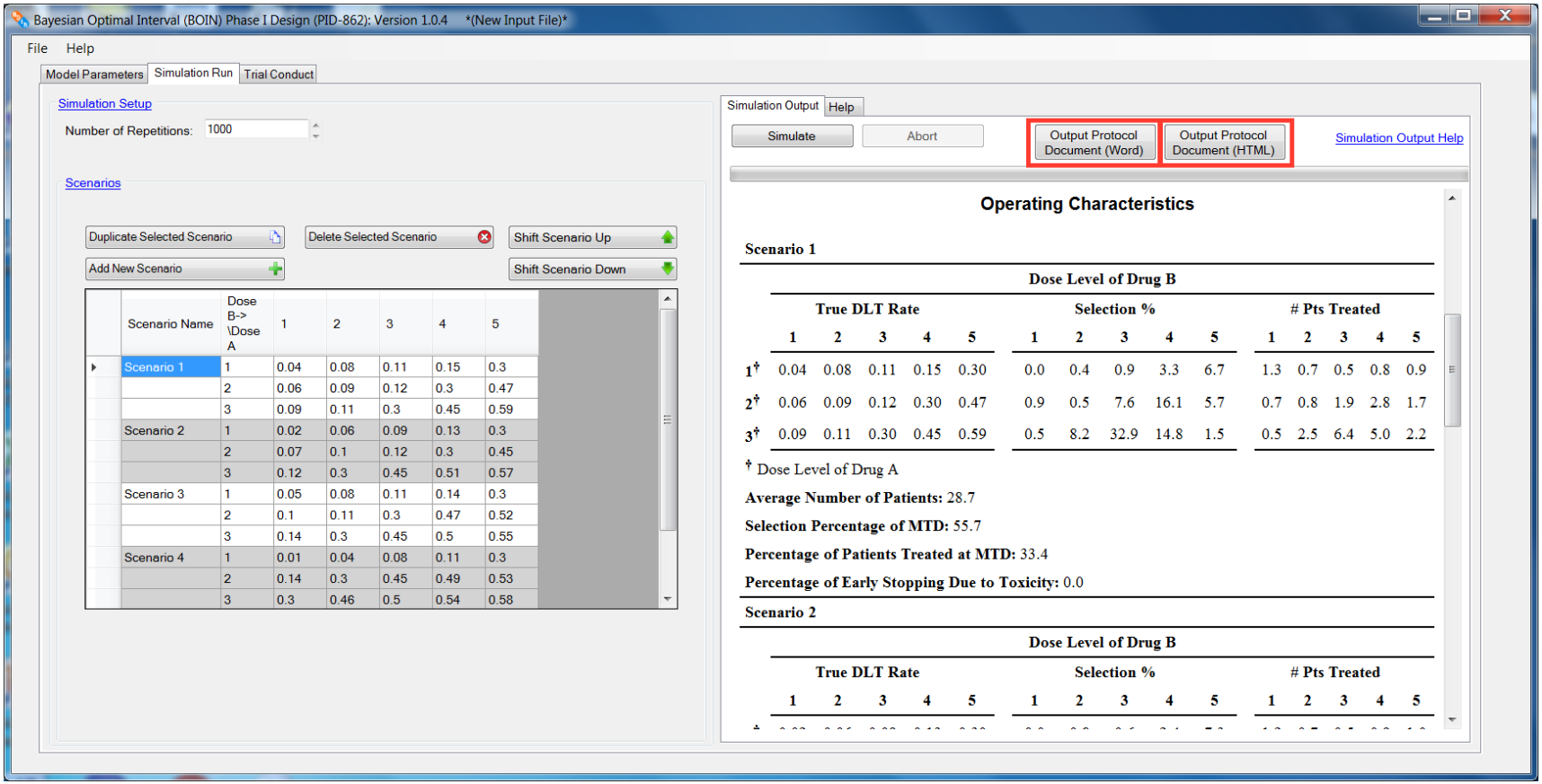
Parameter	Value
Number of Doses - Drug A	3
Starting Dose - Drug A	1
Number of Doses - Drug B	5
Starting Dose - Drug B	1
Max sample size	30
Cohort size	1
Stop trial if # patients assigned to single dose reaches	15
Target Toxicity Probability	0.3
Acceptable Toxicity - Upper Bound	0.42
Acceptable Toxicity - Lower Bound	0.18
Eliminate Dose Threshold (pE)	0.95
Number of Repetitions	1000

BOIN Desktop Program



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

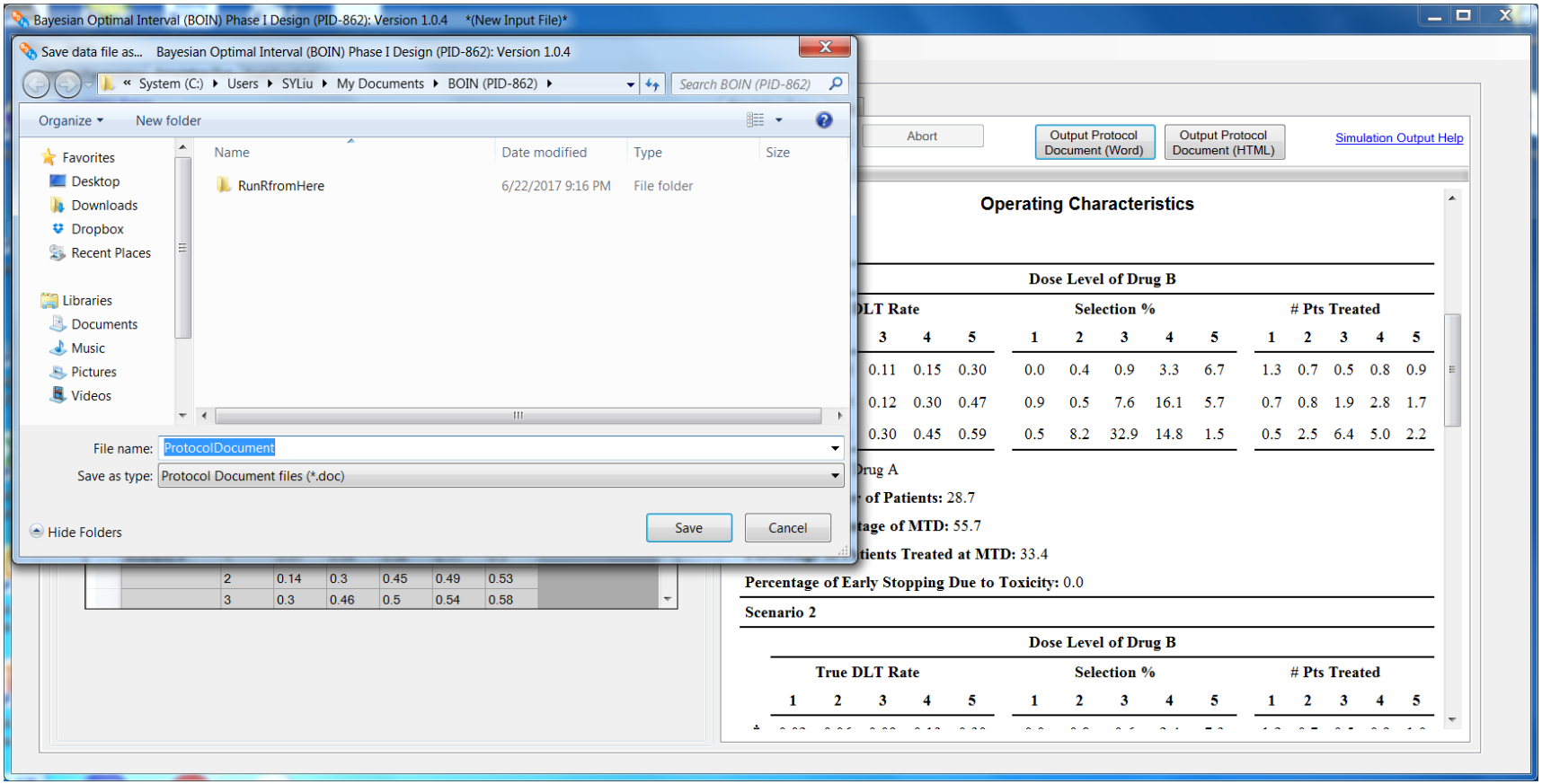
BOIN Desktop Program



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

	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	0.9	3.3	6.7	1.3	0.7	0.5	0.8	0.9
2†	0.06	0.09	0.12	0.30	0.47	0.9	0.5	7.6	16.1	5.7	0.7	0.8	1.9	2.8	1.7
3†	0.09	0.11	0.30	0.45	0.59	0.5	8.2	32.9	14.8	1.5	0.5	2.5	6.4	5.0	2.2

BOIN Desktop Program



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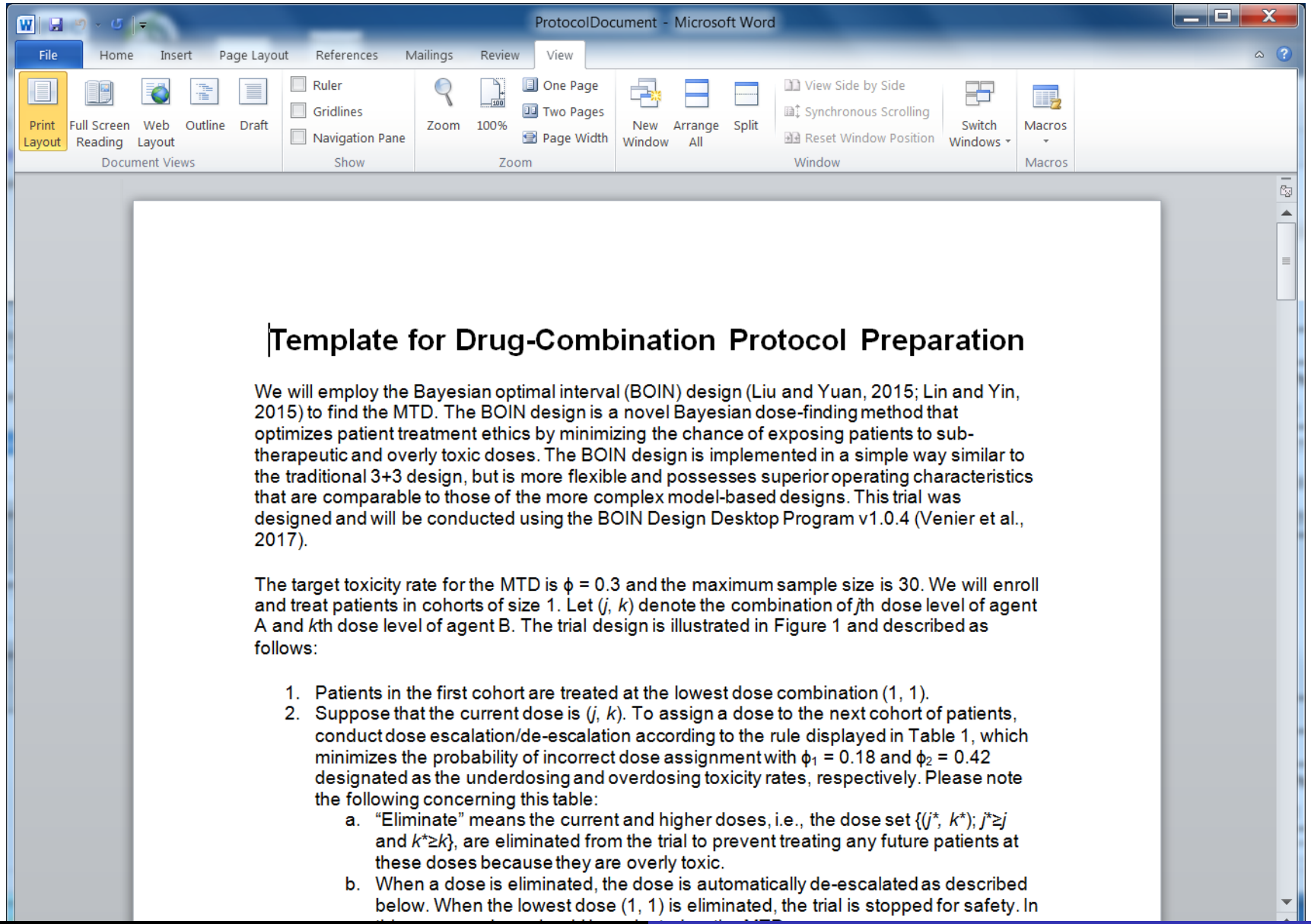


Template for Drug-Combination Protocol Preparation

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 v1.0.4 (Venier et al., 2017).

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:

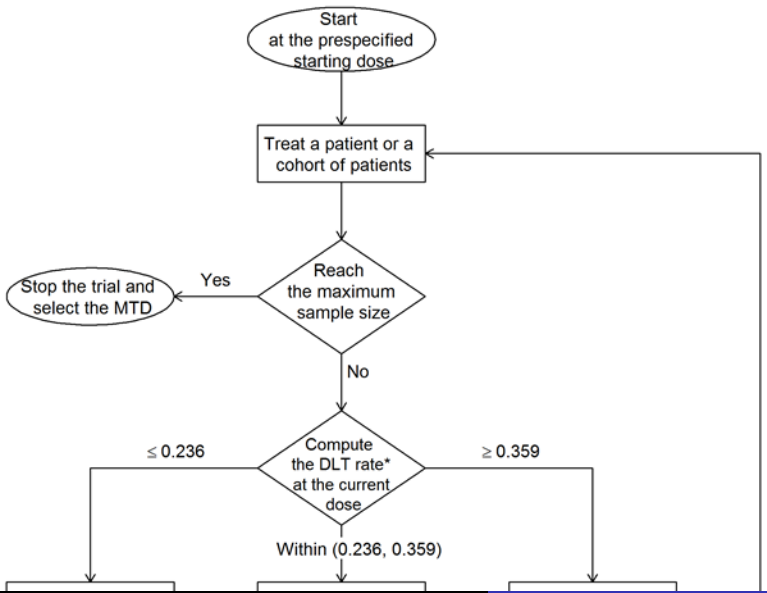
1. Patients in the first cohort are treated at the lowest dose combination (1, 1).
2. Suppose that the current dose is (j, k). To assign a dose to the next cohort of patients, conduct dose escalation/de-escalation according to the rule displayed in Table 1, which minimizes the probability of incorrect dose assignment with $\phi_1 = 0.18$ and $\phi_2 = 0.42$ designated as the underdosing and overdosing toxicity rates, respectively. 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

BOIN Desktop Program

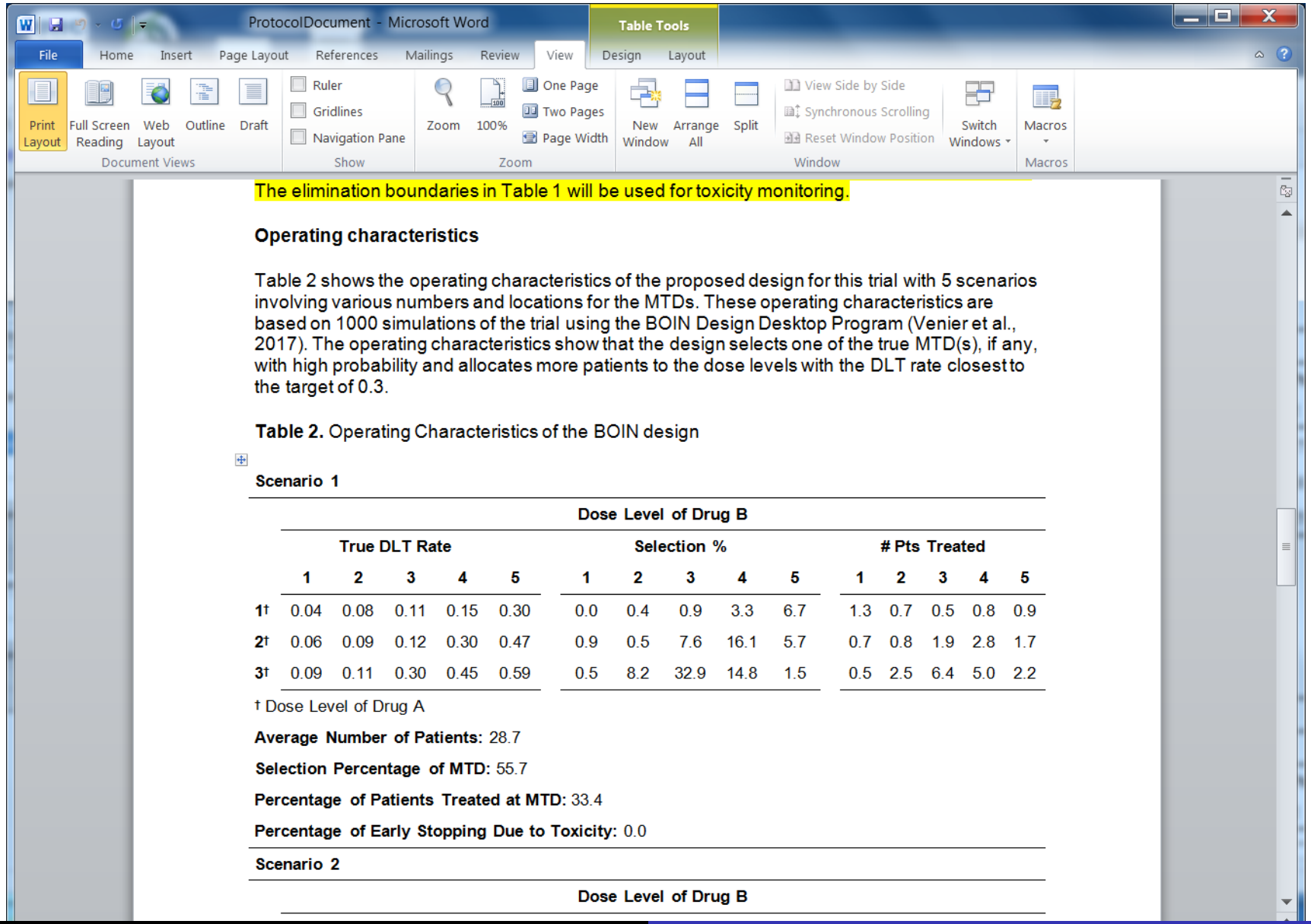
ProtocolDocument - Microsoft Word

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



BOIN Desktop Program



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The elimination boundaries in Table 1 will be used for toxicity monitoring.

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., 2017). 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	0.9	3.3	6.7	1.3	0.7	0.5	0.8	0.9
2†	0.06	0.09	0.12	0.30	0.47	0.9	0.5	7.6	16.1	5.7	0.7	0.8	1.9	2.8	1.7
3†	0.09	0.11	0.30	0.45	0.59	0.5	8.2	32.9	14.8	1.5	0.5	2.5	6.4	5.0	2.2

† Dose Level of Drug A

Average Number of Patients: 28.7

Selection Percentage of MTD: 55.7

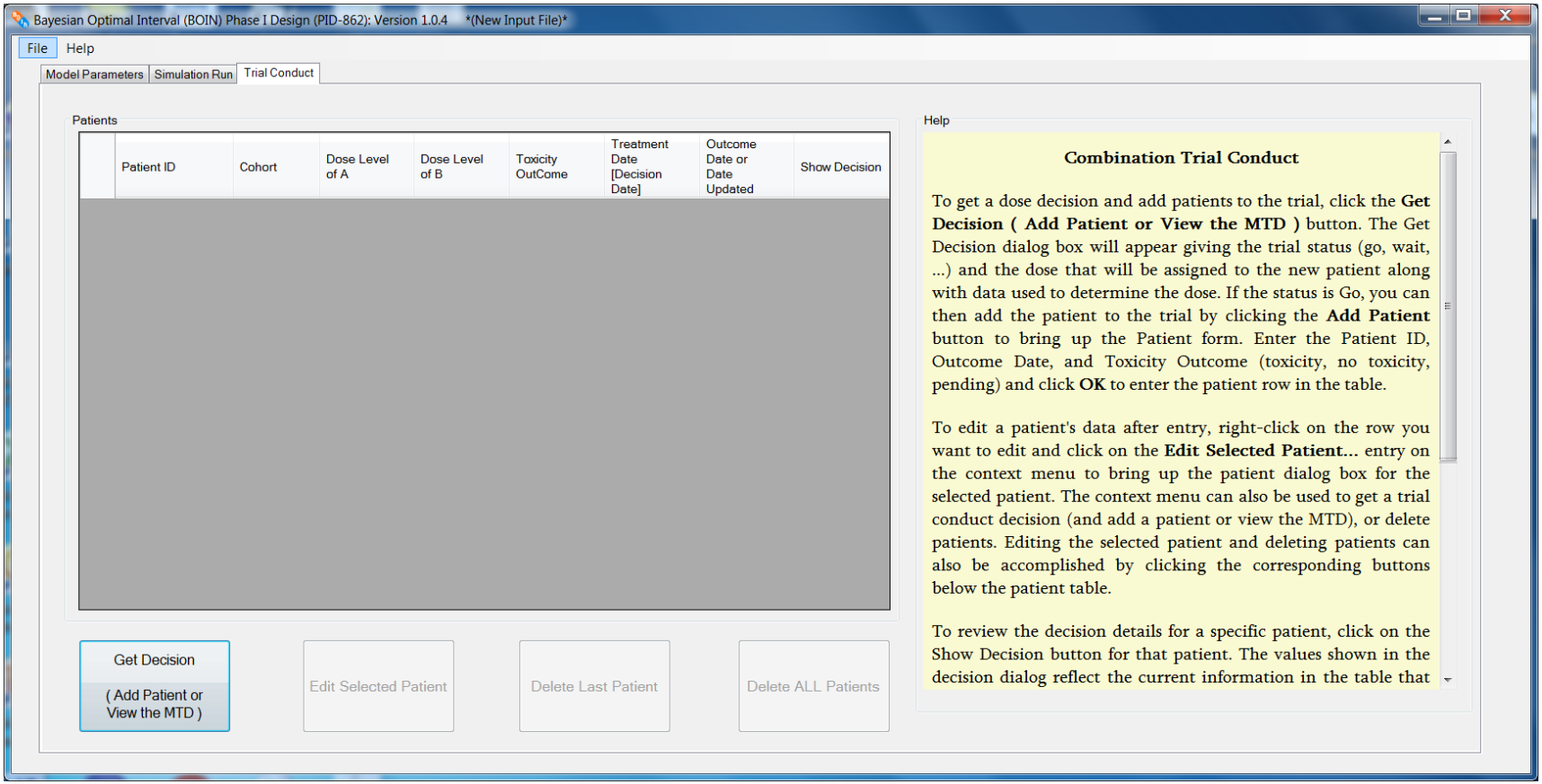
Percentage of Patients Treated at MTD: 33.4

Percentage of Early Stopping Due to Toxicity: 0.0

Scenario 2

	Dose Level of Drug B

BOIN Desktop Program



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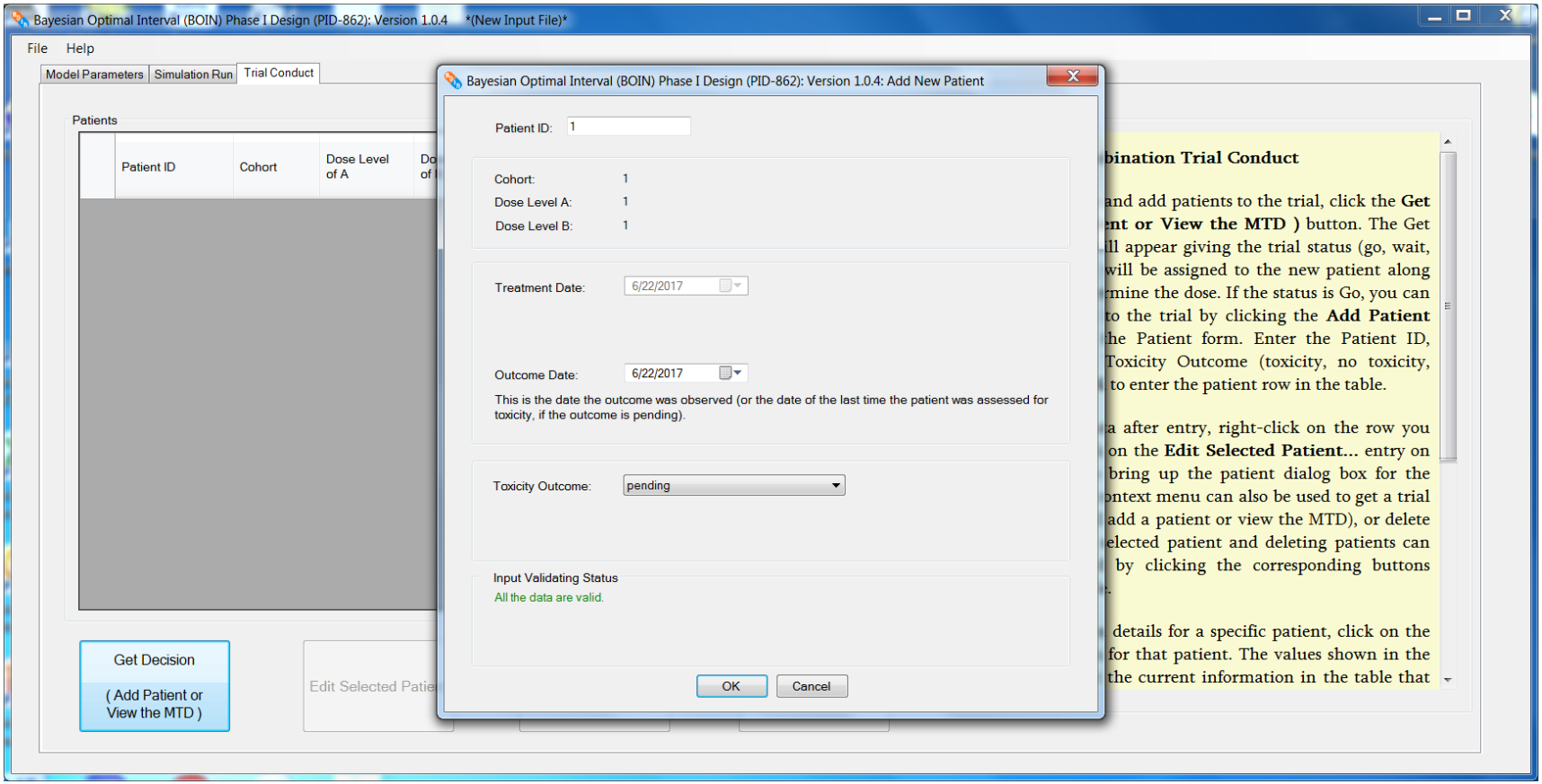

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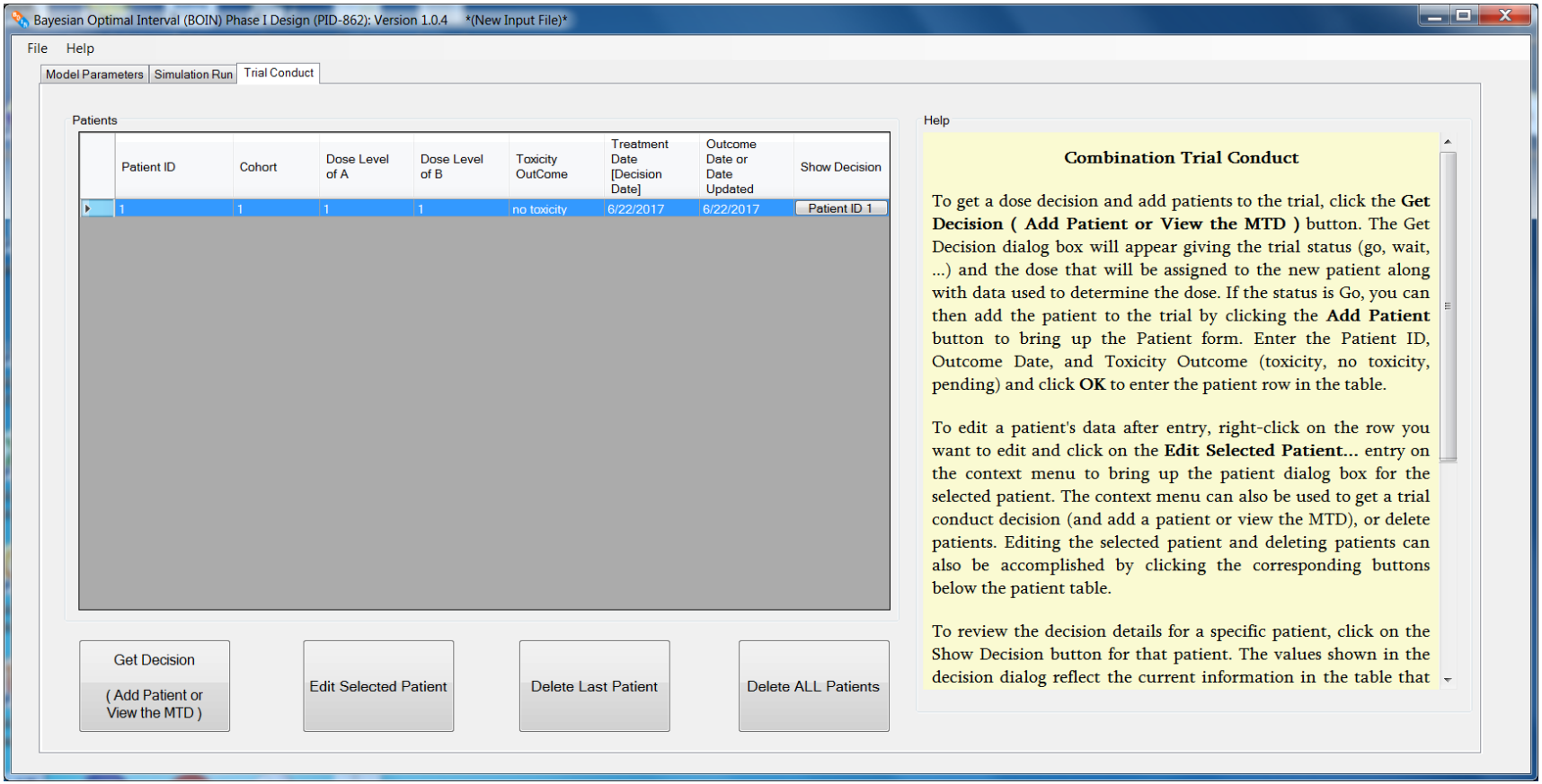

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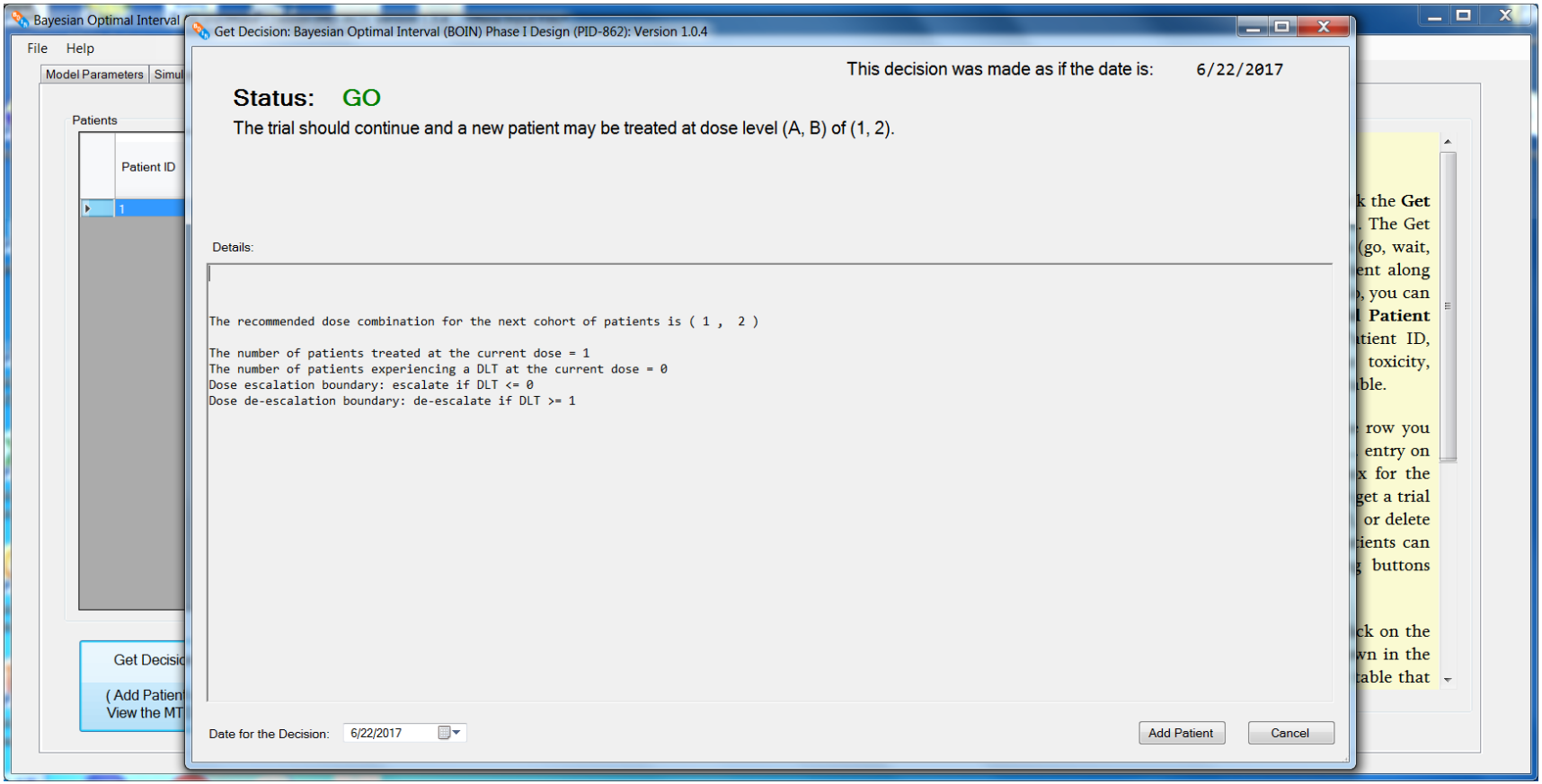

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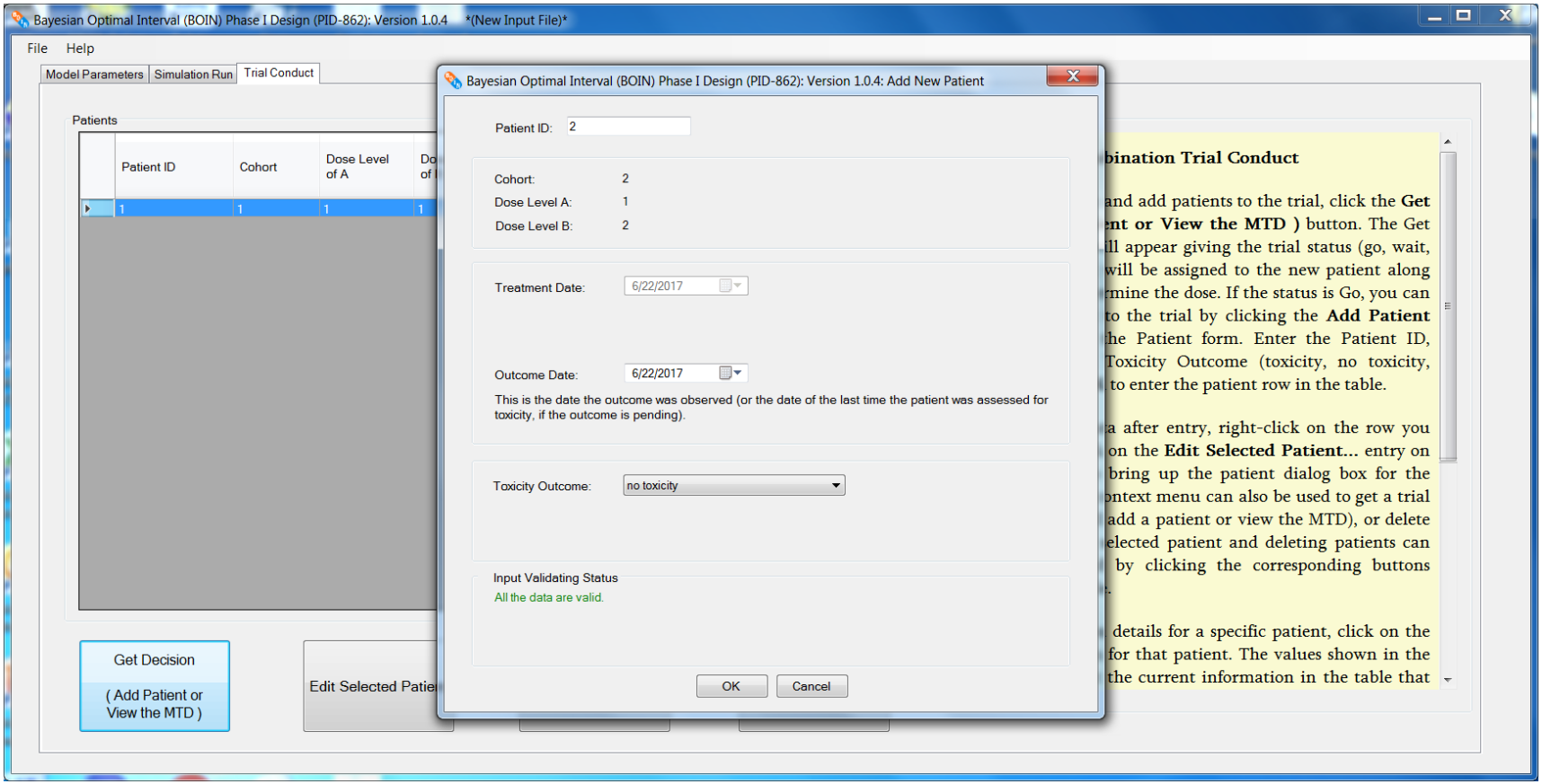

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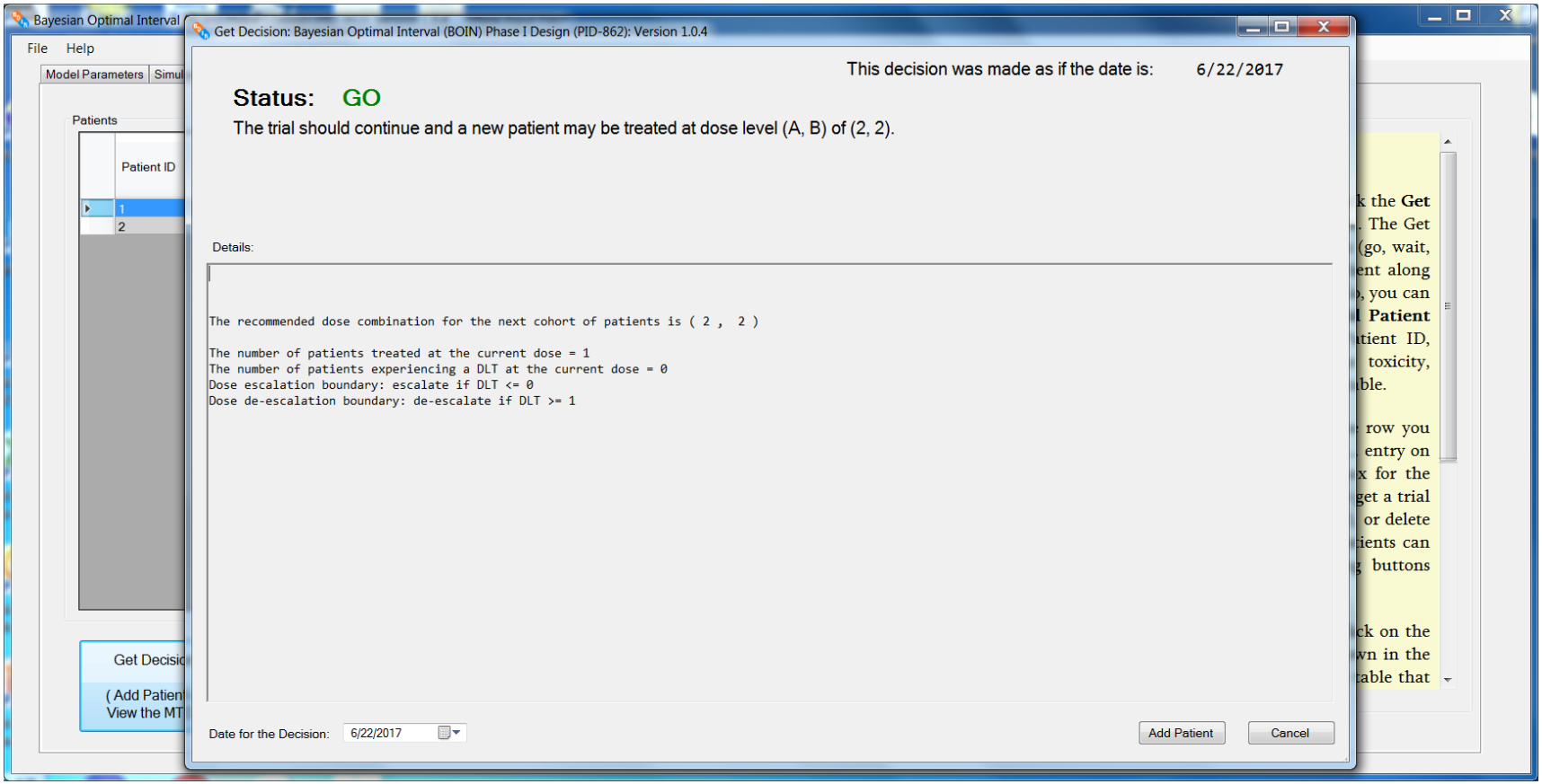

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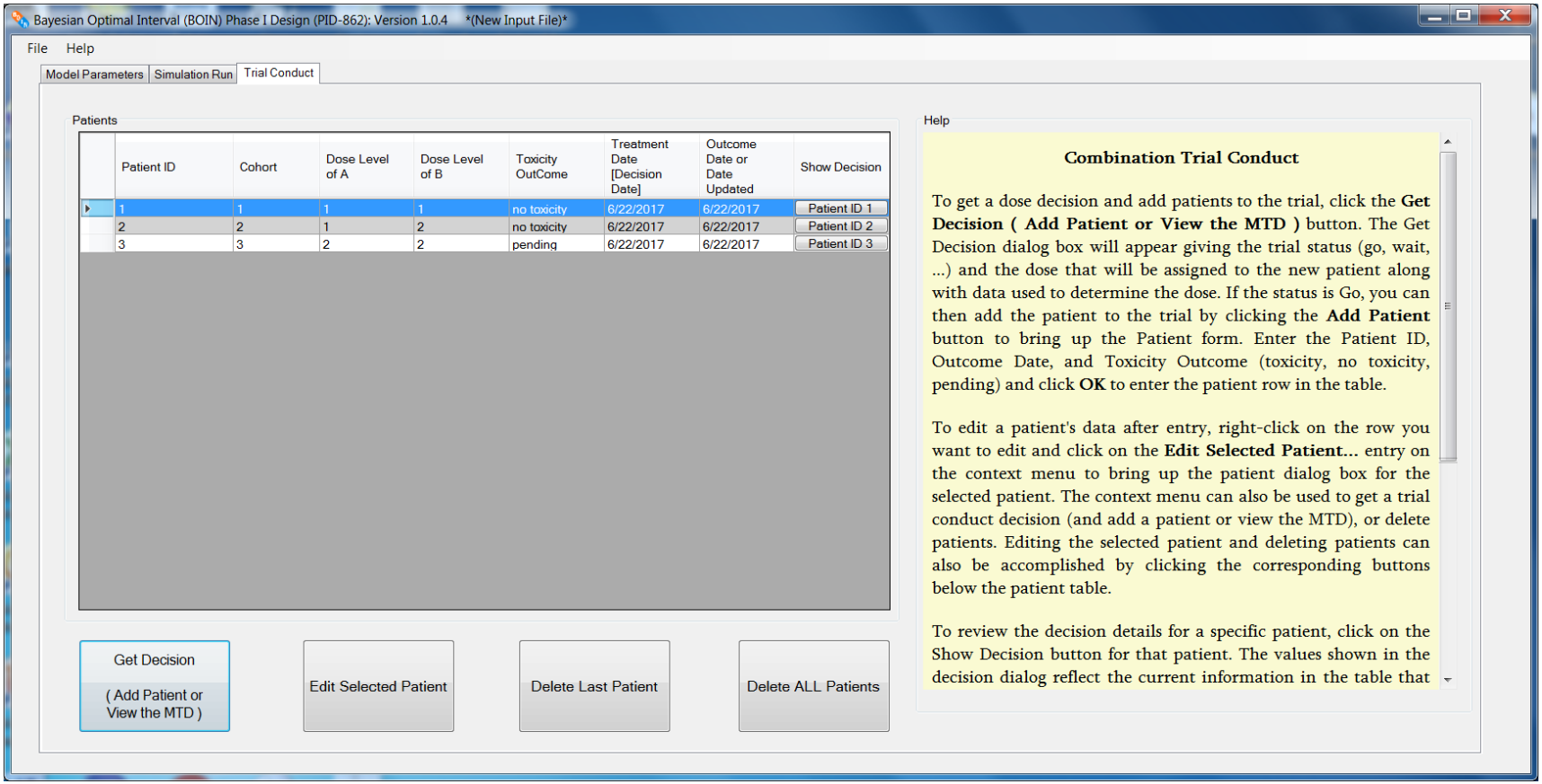
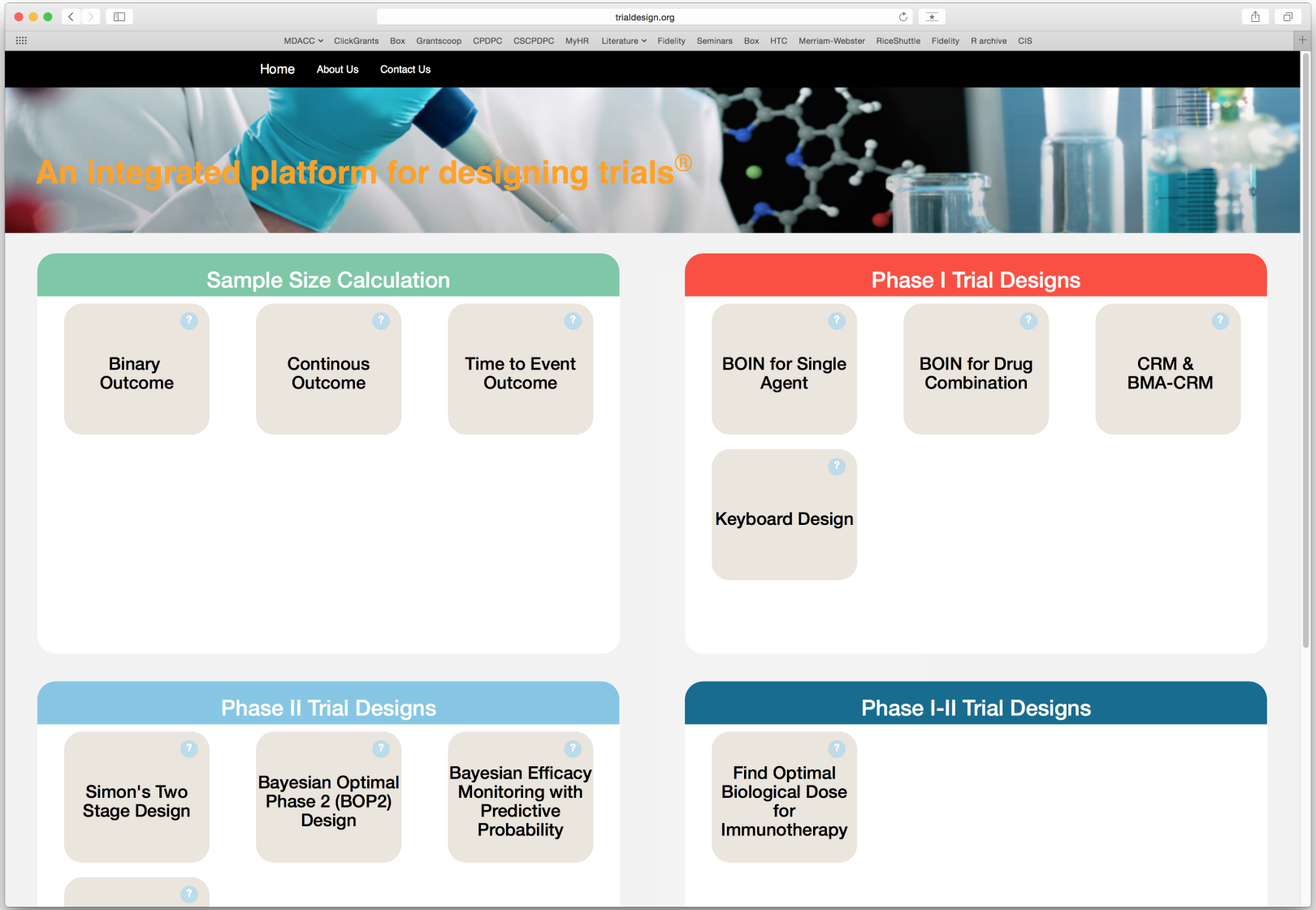


Online app

http://www.trialdesign.org

An integrated platform for designing clinical trials

Online app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Time to Event Outcome
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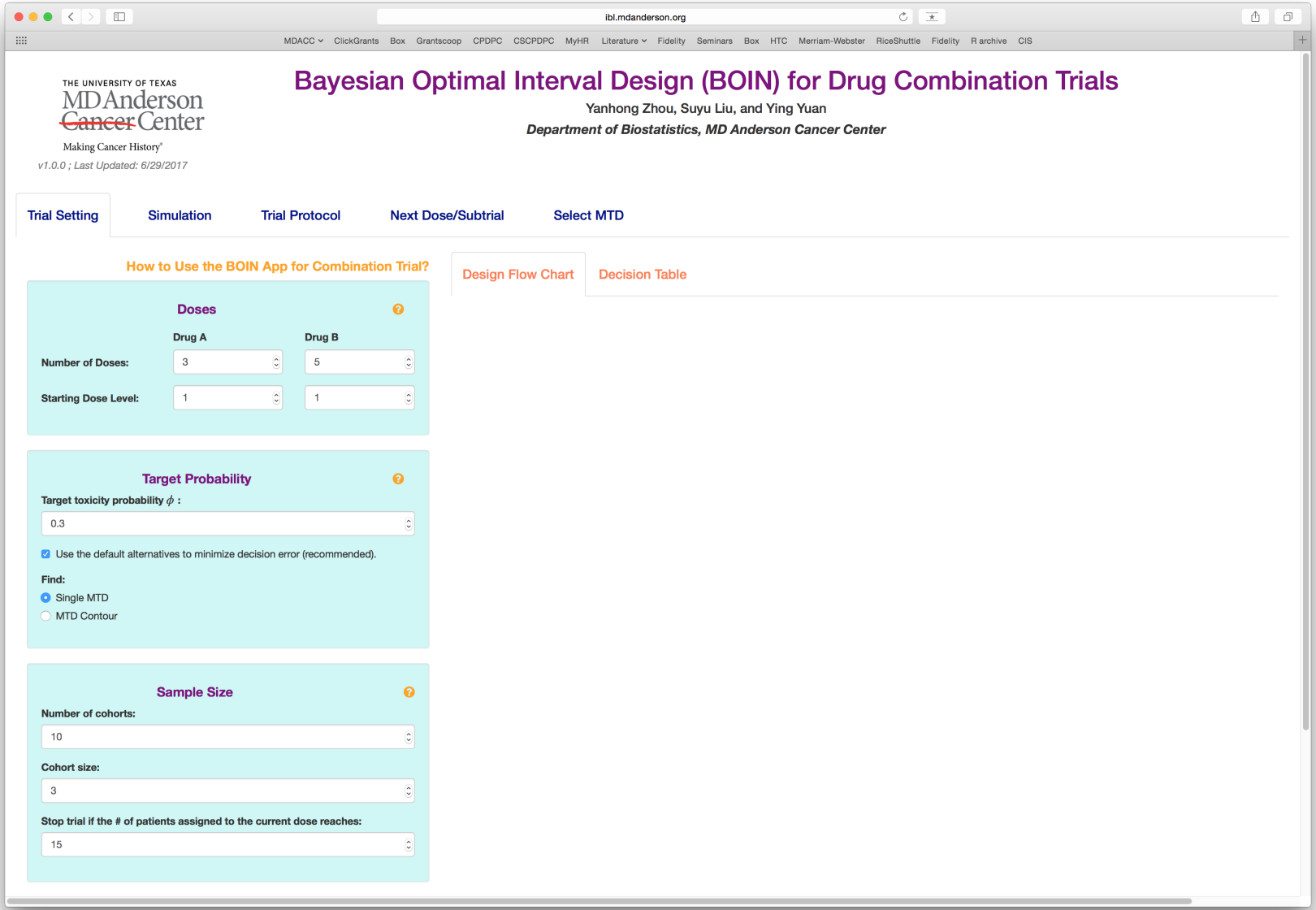
BOIN for Single Agent
BOIN for Drug Combination
CRM & BMA-CRM
Keyboard Design
Phase II Trial Designs
Simon's Two Stage Design
Bayesian Optimal Phase 2 (BOP2) Design
Bayesian Efficacy Monitoring with Predictive Probability
Phase I-II Trial Designs
Find Optimal Biological Dose for Immunotherapy

Online app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Making Cancer History®
v1.0.0 ; Last Updated: 6/29/2017
Bayesian Optimal Interval Design (BOIN) for Drug Combination Trials
Yanhong Zhou, Suyu Liu, and Ying Yuan
Department of Biostatistics, MD Anderson Cancer Center
Trial Setting
Simulation
Trial Protocol
Next Dose/Subtrial
Select MTD
How to Use the BOIN App for Combination Trial?
Design Flow Chart
Decision Table
Doses
Drug A
Drug B
Number of Doses:
3
5
Starting Dose Level:
1
1
Target Probability
Target toxicity probability ϕ :
0.3
Use the default alternatives to minimize decision error (recommended).
Find:
Single MTD
MTD Contour
Sample Size
Number of cohorts:
10
Cohort size:
3
Stop trial if the # of patients assigned to the current dose reaches:
15

Summary

- The BOIN drug-combination design provides a simple, robust, well-performing approach to find a MTD
- The BOIN design can also be used to find the MTD contour (Zhang and Yuan, 2016)
- Easy-to-use software is freely available to implement the BOIN combination designs
- The R package "BOIN" can also be used to design seamless phase I-II combination trials

References

- Yuan, Y. and Zhang, L. (2017) Designing Early-Phase Drug Combination Trials. *Handbook of Methods for Designing, Monitoring, and Analyzing Dose Finding Trials*, edited by O'Quigley J., Iasonos, A and Bornkamp, B., Chapter 6, p109-p126.
- Yuan, Y., Hess, K., Hilsenbeck, S. and Gilbert M. (2016) Bayesian optimal interval design: a simple and well-performing design for phase I oncology trials *Clinical Cancer Research*, 22, 4291-430.
- Lin R. and Yin G. (2016) Bayesian Optimal Interval Designs for Dose Finding in Drug-combination Trials, *Statistical Methods in Medical Research*, in press
- Zhang, L. and Yuan, Y. (2016) A Practical Bayesian Design to Identify the Maximum Tolerated Dose Contour for Drug Combination Trials. *Statistics in Medicine*, 35, 4924-4936.
- Yuan, Y. and Yin, G. (2011) Bayesian phase I/II drug-combination trial design in oncology. *Annals of Applied Statistics*, 5, 924-942.

Thank you !

Backup slides

Finding the MTD contour

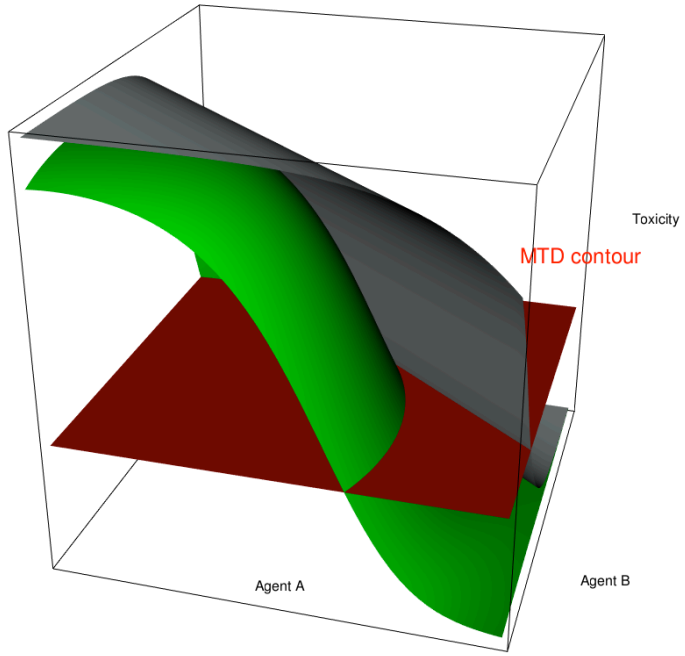
- Finding the MTD contour (or multiple MTDs) is of intrinsic interest to many combination trials.
  - There are multiple MTDs in the dose matrix. Hard to justify a single one as the target.
  - Finding multiple MTDs provides us an opportunity to find the optimal synergistic treatment effect, e.g., identify the MTD with the highest synergistic treatment effect in subsequent phase II trials.

Finding the MTD contour is more challenging

- Much more challenging than finding a single MTD.
- In order to find all MTDs in the dose matrix, we must explore the whole dose matrix using a limited sample size; otherwise, we risk missing some MTDs
- More susceptible to model misspecification

Robustness is an issue

- To find the MTD contour, we must estimate the whole MTD contour correctly.
- In contrast, to find a single MTD, a good local fit to a MTD is adequate.



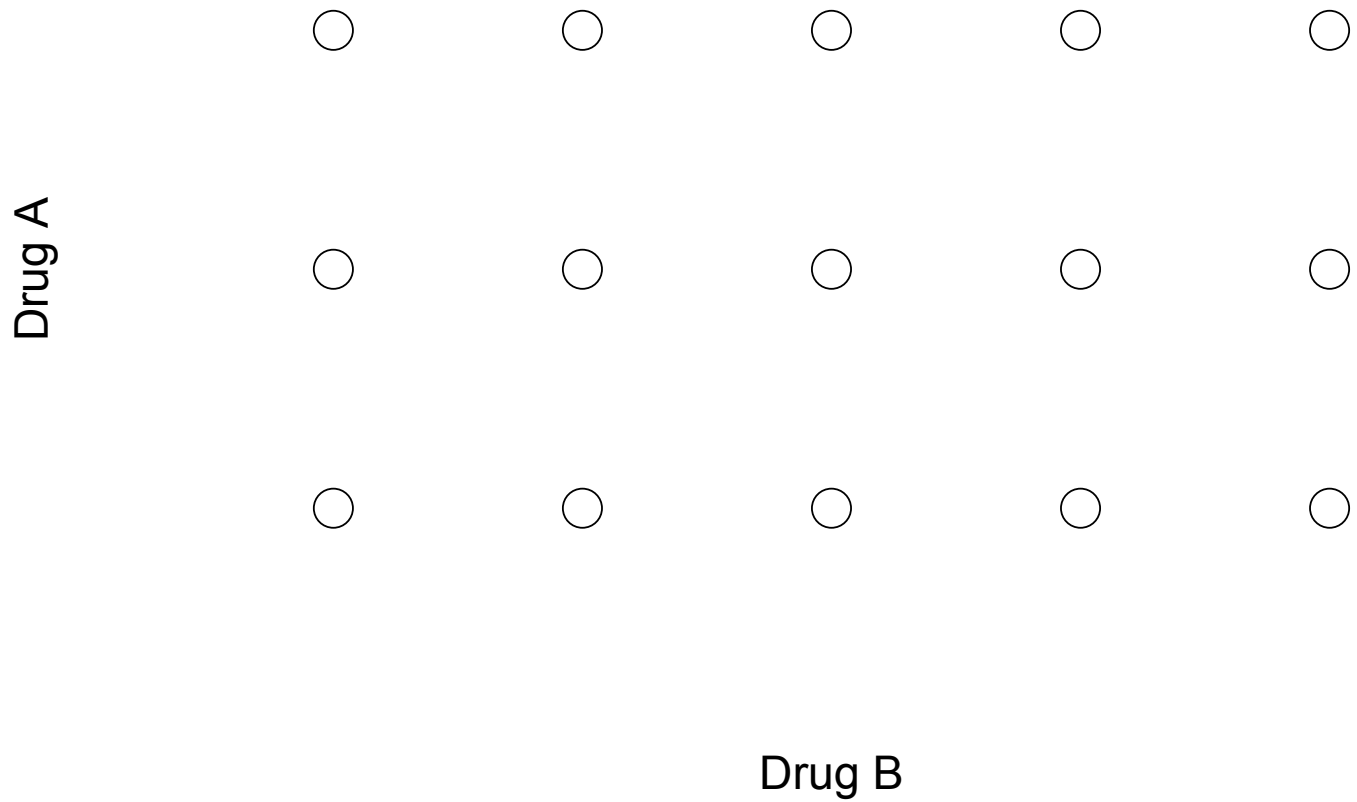
Finding the MTD contour

- Several designs have been proposed to find the MTD contour (e.g., Thall et al. 2003, Yuan and Yin, 2009; Mander and Sweeting, 2015; Zhang and Yuan, 2016).
- We focus on the waterfall design (Zhang and Yuan, 2016), which is well-performing and easy to implement in practice.

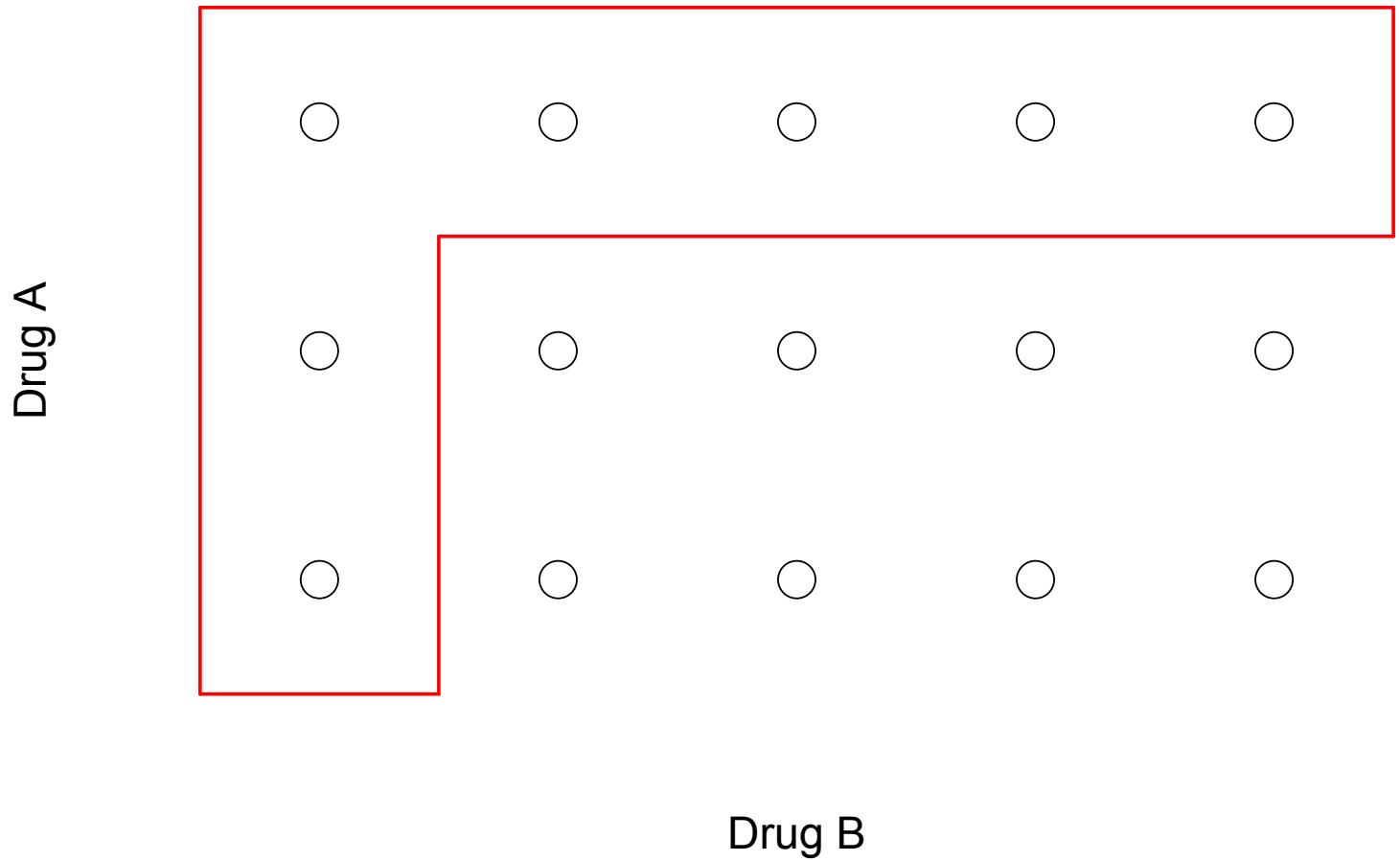
Divide and conquer

- Waterfall design takes the divide and conquer strategy (Yuan and Yin, 2008)
- Partition the dose matrix into a series of blocks (i.e., groups of doses), within which the doses are fully ordered, and then find the MTD within each block.
- Each block is called a “subtrial"
- We conduct each subtrial using the BOIN design

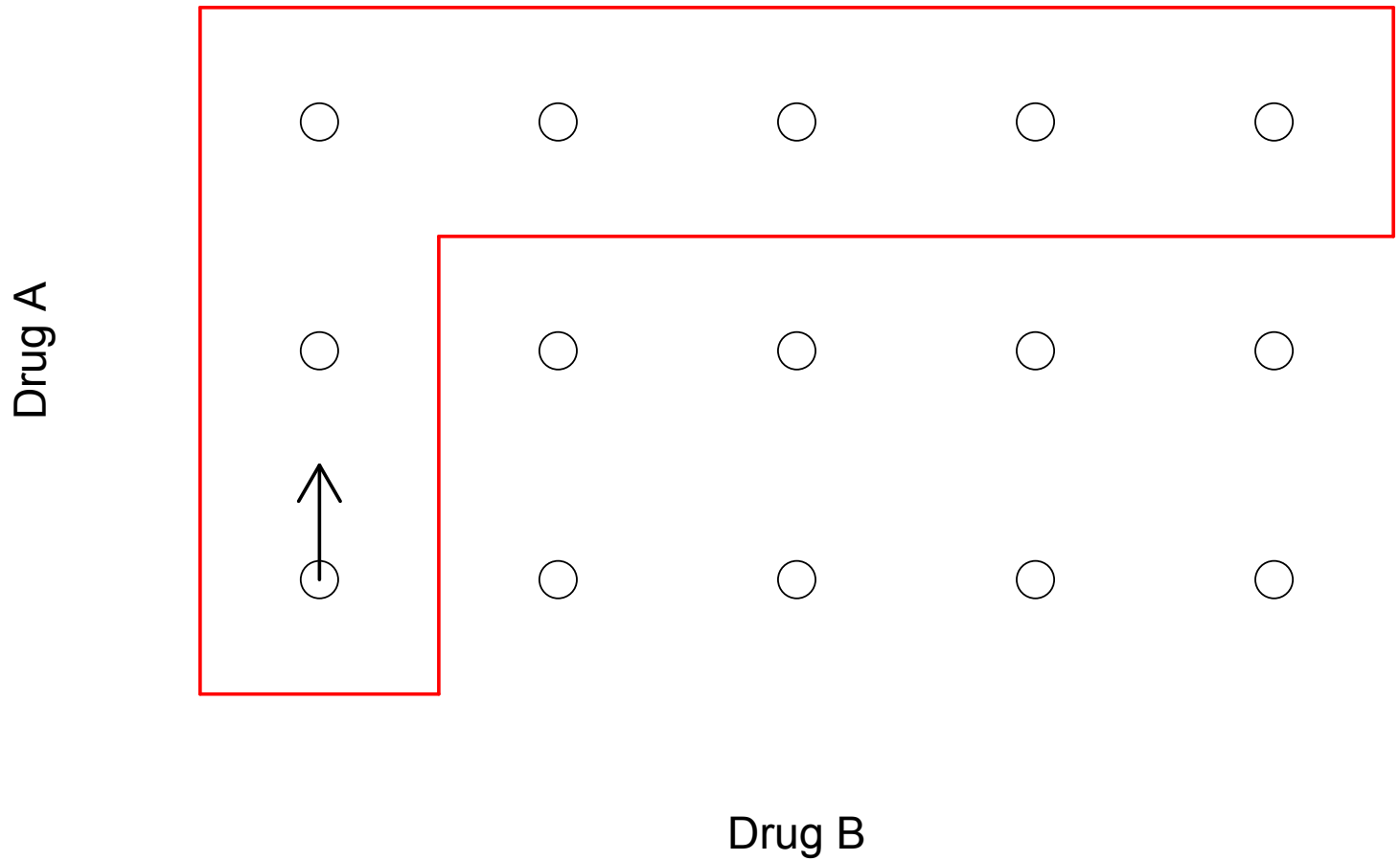
Waterfall design



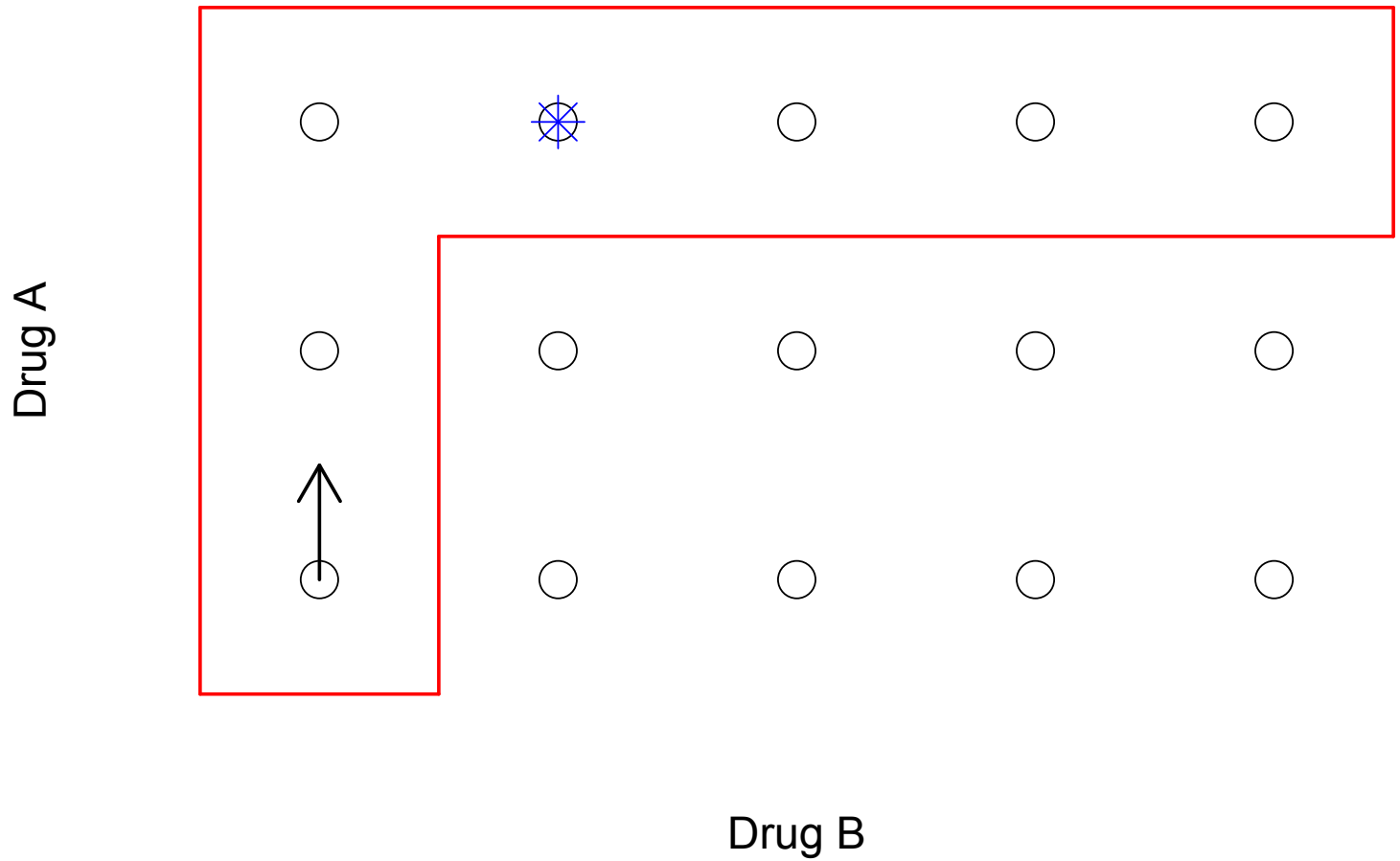
Waterfall design



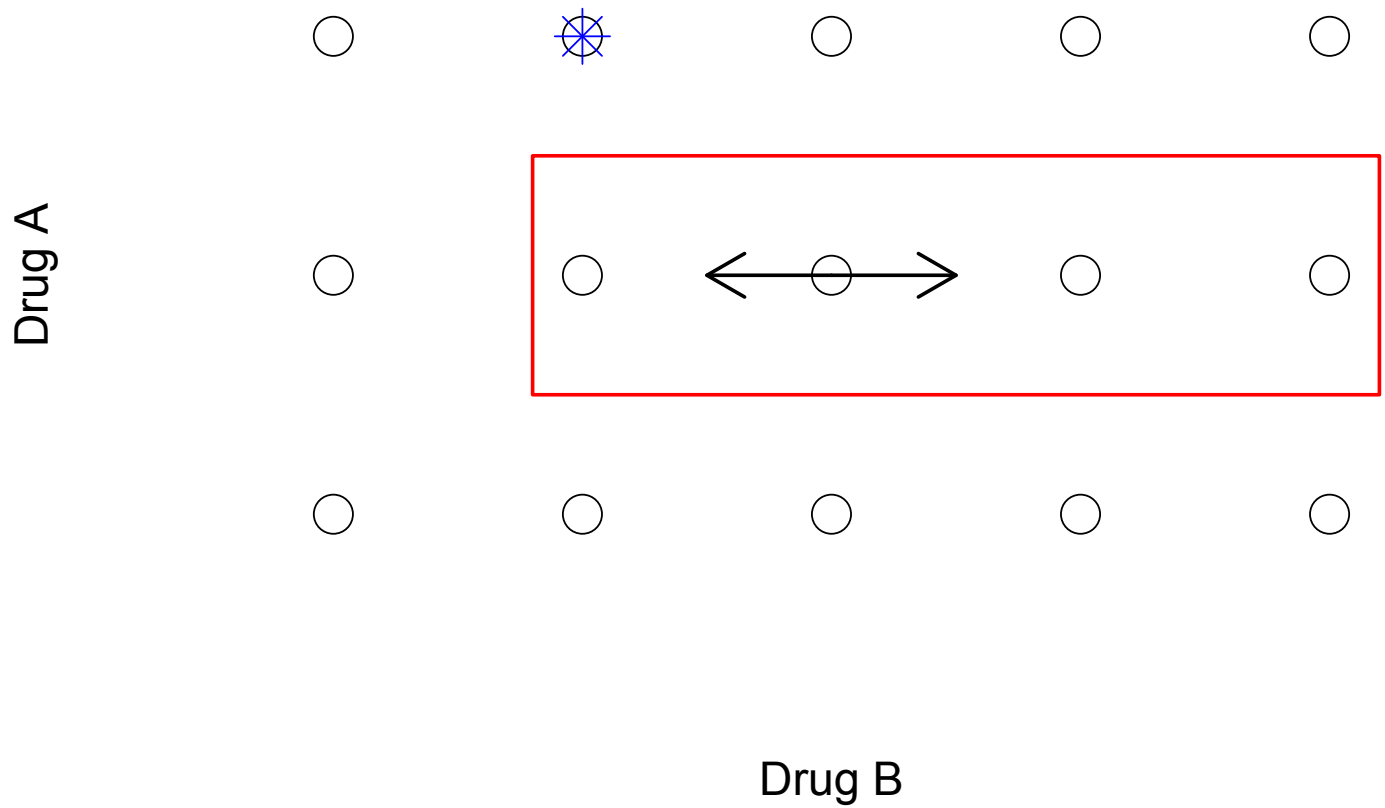
Waterfall design



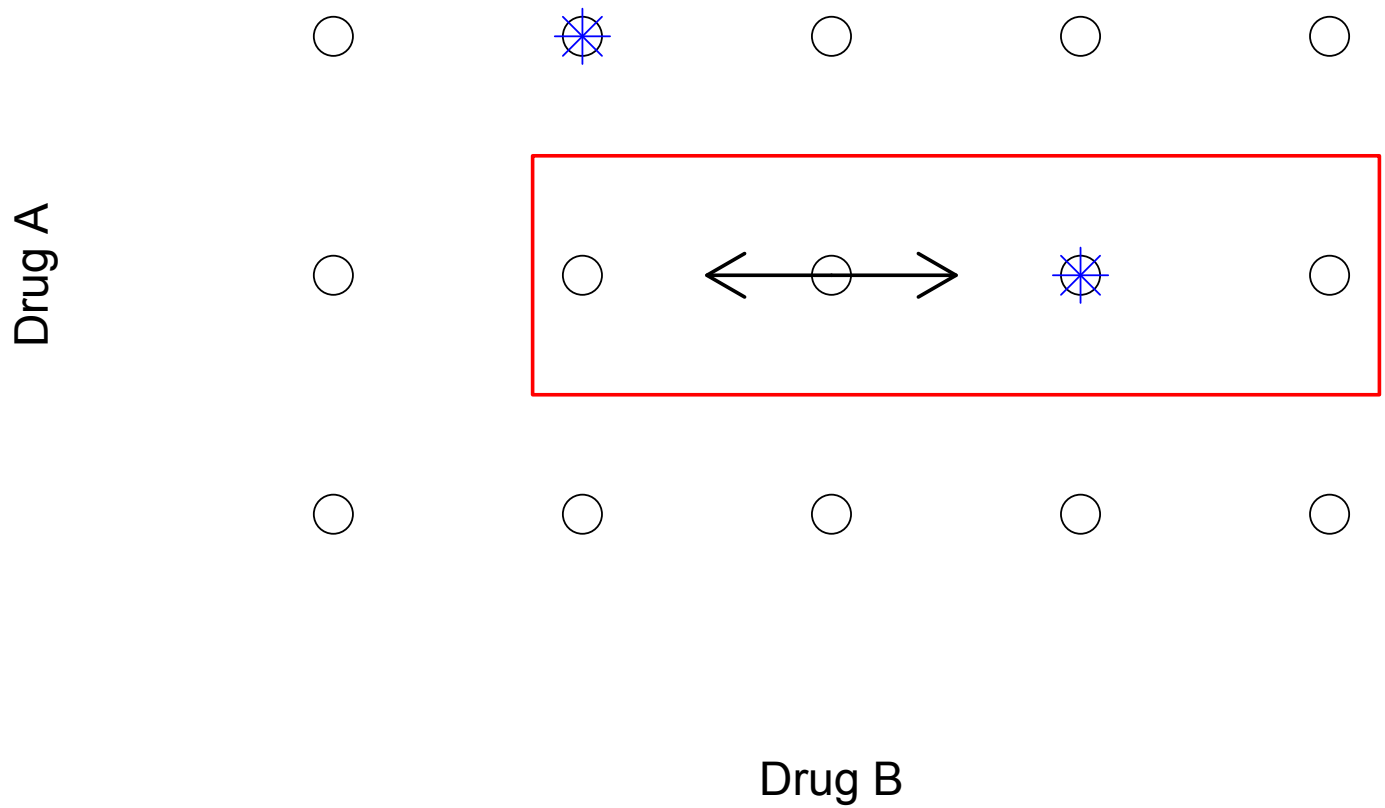
Waterfall design



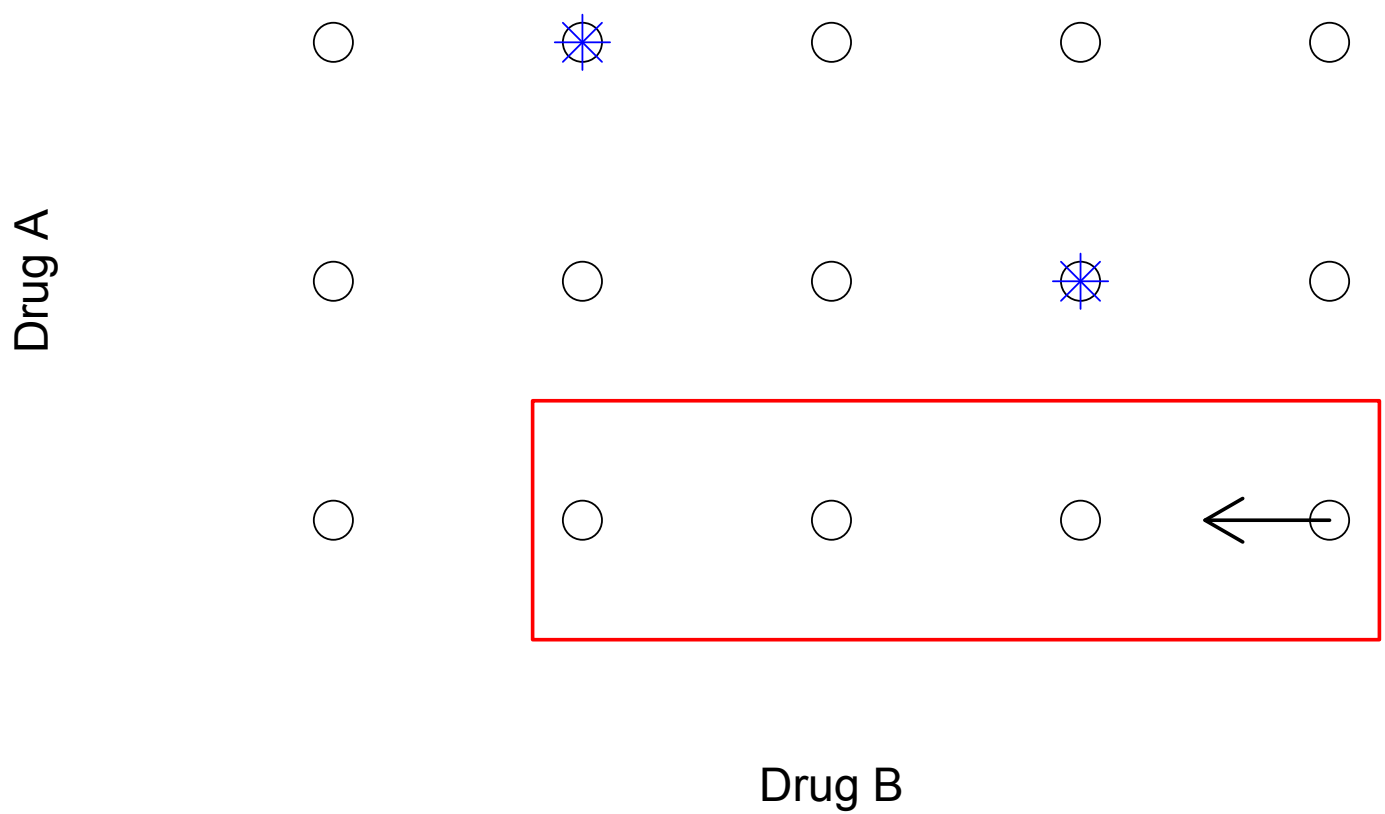
Waterfall design



Waterfall design



Waterfall design



Waterfall design