Design and Sample Size Determination for Multiple-dose Randomized Phase II Trials for Dose Optimization

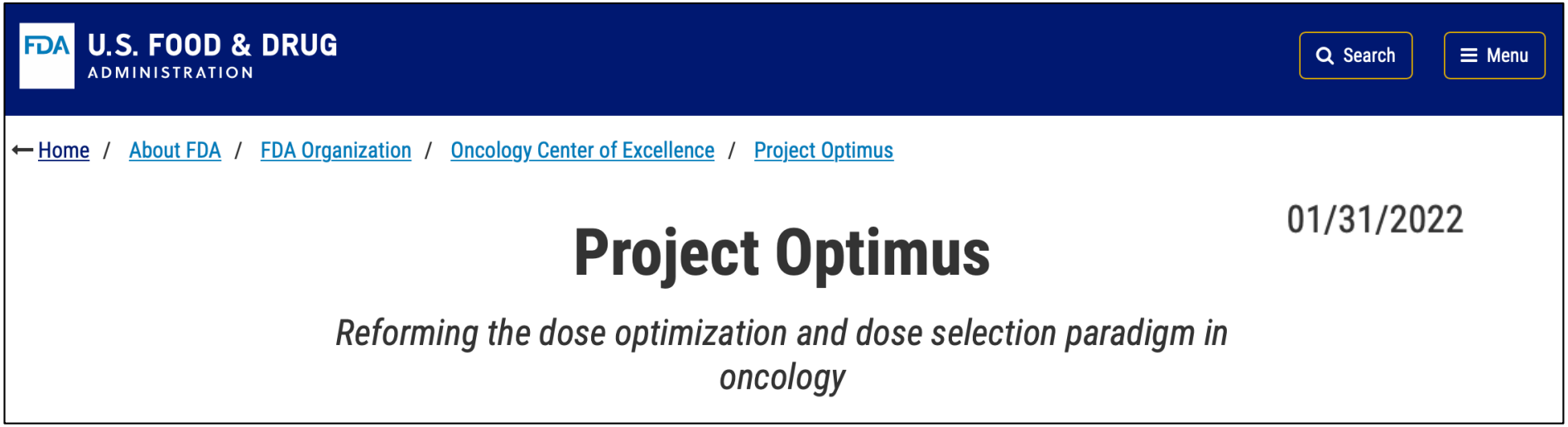
Ying Yuan, PhD

The University of Texas MD Anderson Cancer Center

Joint work with Peng Yang (Rice U), Daniel Li (BMS), Ruitao Lin (MD Anderson), and Bo Huang (Pfizer)

Project Optimus

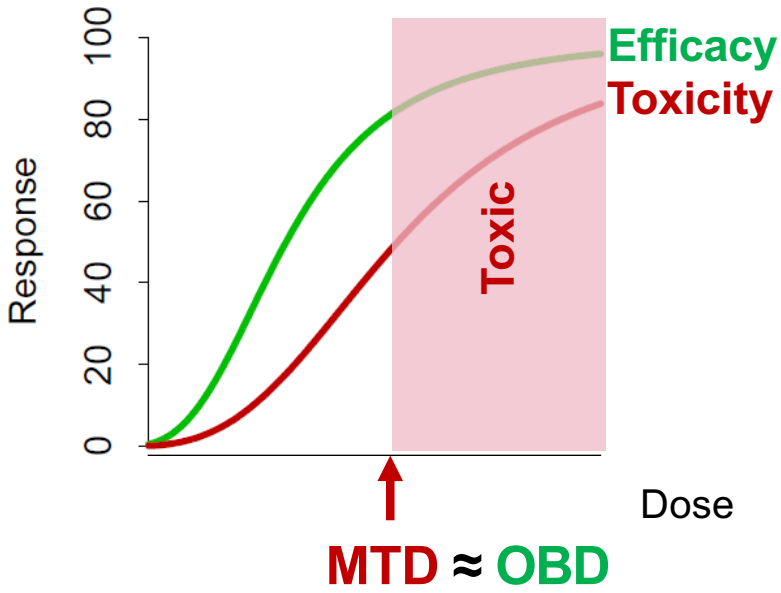
- In 2022, FDA OCE initiated Project Optimus “ to reform the dose optimization and dose selection paradigm in oncology drug development.”



Paradigm shifting from MTD to OBD

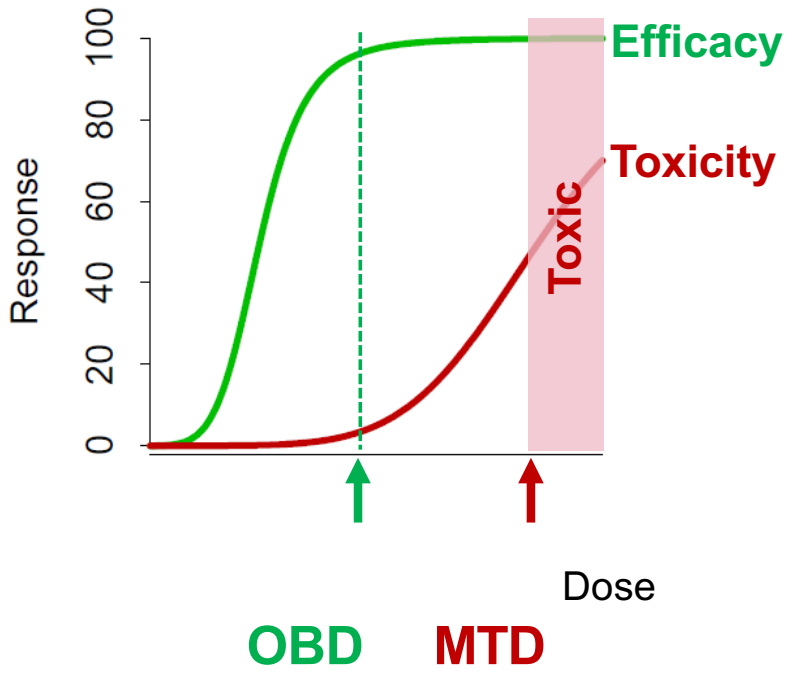
Cytotoxic Chemotherapy

Narrow Therapeutic Index



Targeted Therapies

Wide Therapeutic Index



- MTD-based dose finding is often appropriate to inform RP2D

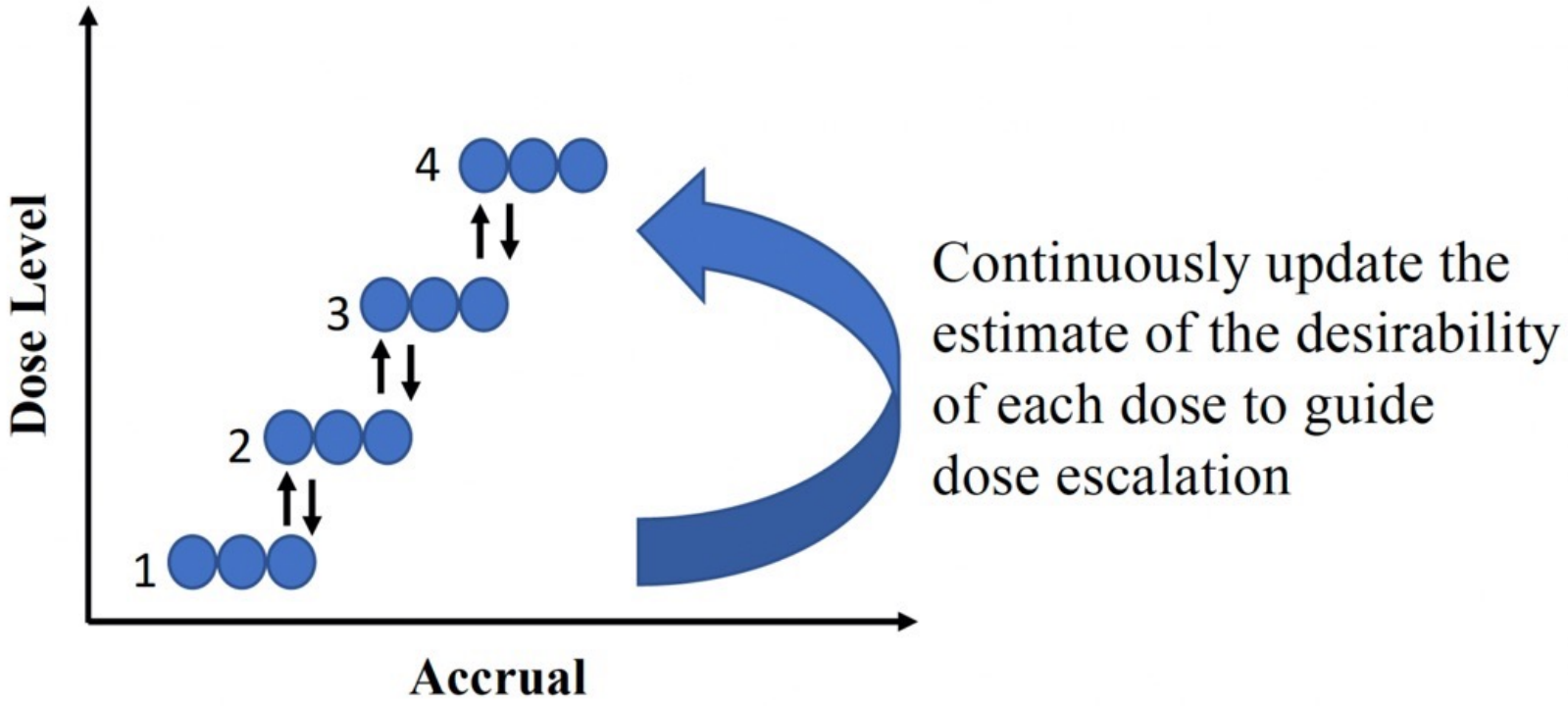
- Safety alone is not sufficient to inform optimal RP2D

MTD: maximum tolerated dose.

OBD: optimal biological dose

Design strategies to find OBD

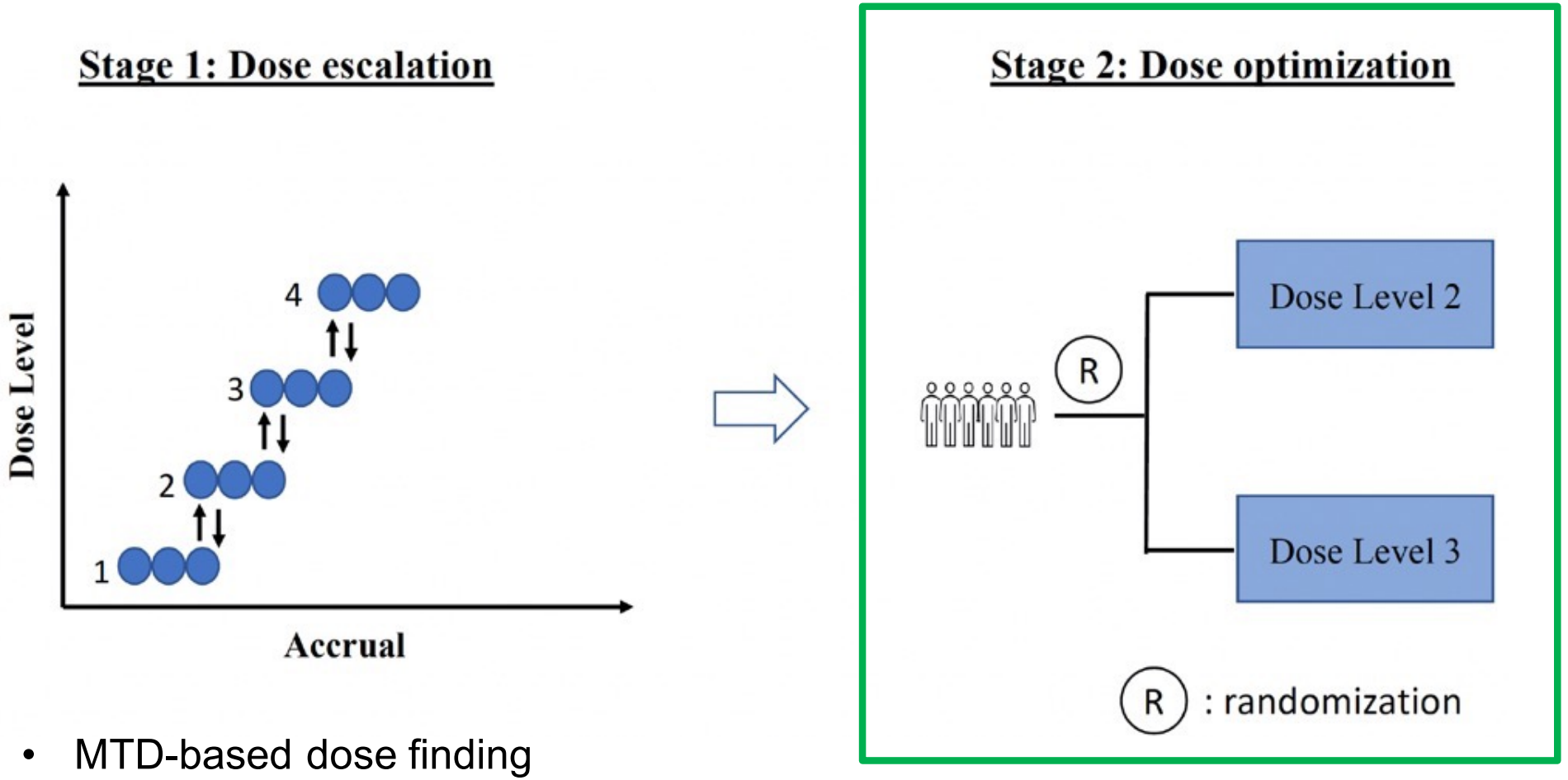
(A) Efficacy-integrated dose-finding strategy



Examples: EffTox/Lo-EffTox (model-based), BOIN12 (model-assisted), among others.

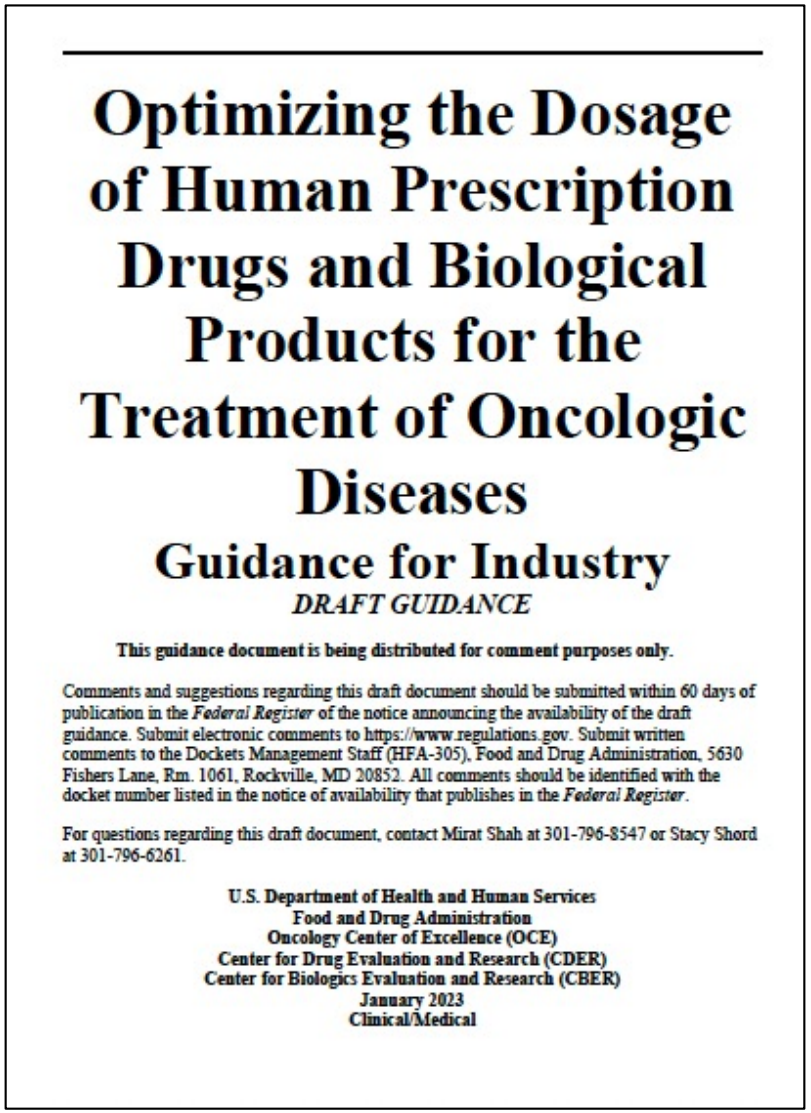
Design strategies to find OBD

(B) Two-stage dose-finding strategy



- MTD-based dose finding design is often appropriate

FDA guidance



Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact Mirat Shah at 301-796-8547 or Stacy Shord at 301-796-6261.

U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence (OCE)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
January 2023
Clinical/Medical

January 2023

FDA guidance

B. Trial Designs to Compare Multiple Dosages

- Multiple dosages should be compared in a clinical trial(s) designed to assess activity, safety, and tolerability to decrease uncertainty with identifying an optimal dosage(s) in a marketing application.

- A recommended trial design to compare these dosages is a randomized, parallel dose-response trial.
  - Randomization when feasible (rather than enrolling patients to non-randomized dosage cohorts) ensures similarity of patients receiving each dosage and interpretability of dose- and exposure-response relationships.
  - The trial should be sized to allow for sufficient assessment of activity, safety, and tolerability for each dosage. The trial does not need to be powered to demonstrate statistical superiority of a dosage or statistical non-inferiority among the dosages.
  - An adaptive design to stop enrollment of patients to one or more dosage arms of a clinical trial following an interim assessment of efficacy and/or safety could be considered.

FDA (2023) Guidance for Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases.

Two-stage decision-making paradigm

1

Determination of OBD admissible set

- The objective is to identify a dose set that satisfy certain safety and efficacy requirements (i.e., OBD admissible set A) based on prespecified toxicity and efficacy endpoints.
- In the subsequent step, the OBD will be selected from A based on the totality of activity, safety and tolerability data.

2

Identification of the OBD

- “Relevant nonclinical and clinical data, as well as the dose- and exposure-response relationships for safety and efficacy should be evaluated to select a dosage(s) for clinical trial(s)” (FDA guidance)
- Unlikely/impossible to formulate statistical decision rules to capture all quantitative and qualitative considerations relevant to the final OBD selection

Two-stage decision-making paradigm

1

Determination of OBD admissible set

- The objective is to identify a dose set that satisfy certain safety and efficacy requirements (i.e., OBD admissible set A) based on prespecified toxicity and efficacy endpoints.
- In the subsequent step, the OBD will be selected from A based on the totality of activity, safety and tolerability data.

2

Identification of the OBD

- Based on the totality of benefit and risk data: “Relevant nonclinical and clinical data, as well as the dose- and exposure-response relationships for safety and efficacy should be evaluated to select a dosage(s) for clinical trial(s)” (FDA guidance)
- Unlikely/impossible to formulate statistical decision rules to capture all quantitative and qualitative considerations relevant to the OBD selection

Goal

1

Determination of OBD admissible set

- The objective is to identify a dose set that satisfy certain safety and efficacy requirements (i.e., OBD admissible set A) based on prespecified toxicity and efficacy endpoints.
- In the subsequent step, the OBD will be selected from A based on the totality of activity, safety and tolerability data.

Goal: formalize the design of this step to ensure that the trial satisfies certain statistical properties, including type I error and power.

Setup

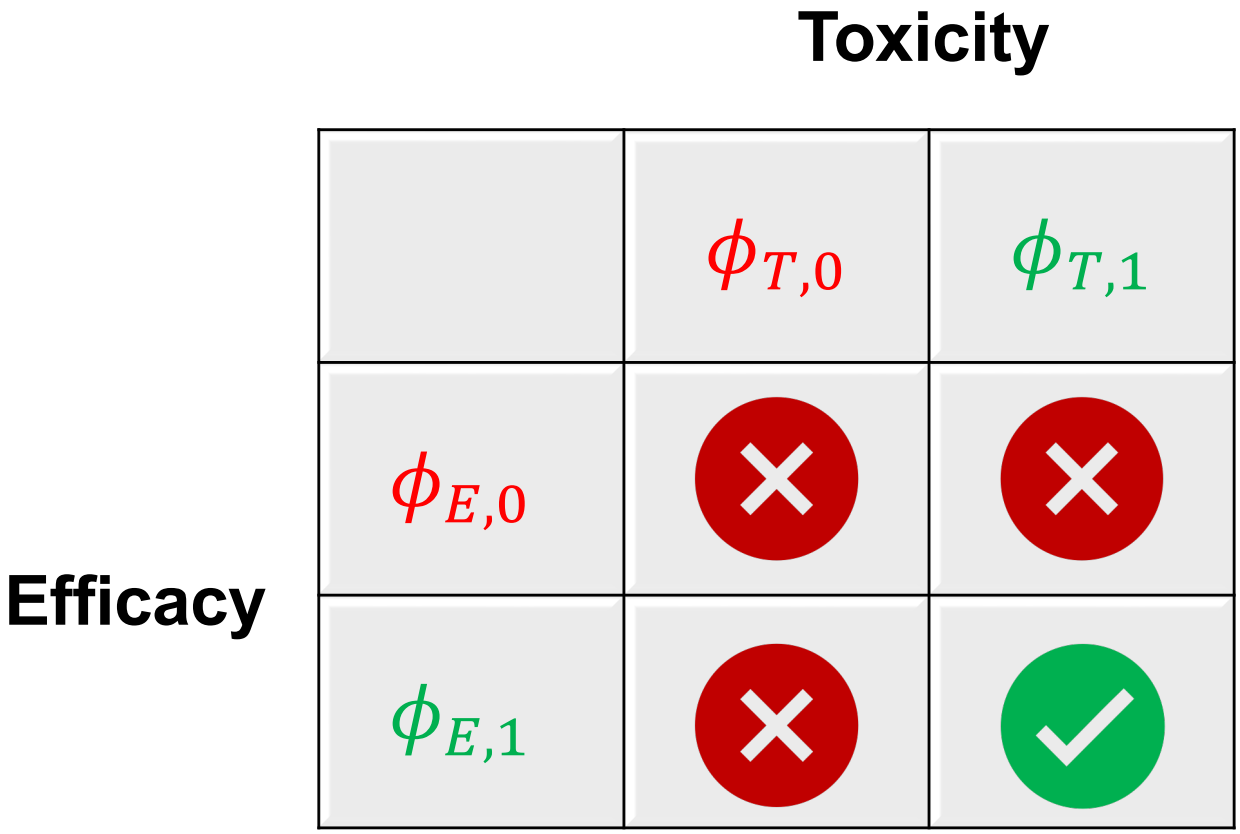
- Consider a multiple-dose randomized trial, where a total of $J \times n$ patients are equally randomized to J doses, $d_1 < d_2 < \cdots < d_J$.
  - In most applications, $J = 2$ or 3, and the highest dose d_J is often the MTD or maximum administered dose
- Let Y_T and Y_E denote binary toxicity and efficacy endpoints, respectively.
  - Example of Y_T: dose-limiting toxicity, dichotomized total toxicity burden, dose tolerability (i.e., discontinuation/reduction/ interruption)
  - Examples of Y_E: objective response, efficacy surrogate endpoints (e.g., pharmacodynamics (PD) endpoints and target receptor occupancy)

Setup

- Let $\pi_{T,j} = \Pr(Y_T = 1 | d_j)$ and $\pi_{E,j} = \Pr(Y_E = 1 | d_j)$ denote the probability of toxicity and efficacy, respectively, for d_j.
- We assume that $\pi_{T,j}$ and $\pi_{E,j}$ are non-decreasing with respect to the dose, while noting that this assumption is not required by our methodology.
- Let $\phi_{T,0}$ denote the null toxicity rate that is high and deemed unacceptable, and $\phi_{T,1}$ denote the alternative toxicity rate that is low and deemed acceptable.
- Similarly, let $\phi_{E,0}$ and $\phi_{E,1}$ denote the null and alternative efficacy rates that are deemed unacceptable and acceptable, respectively.

OBD admissible

- For a given dose,



Hypotheses

- Consider

  H_0: None of the doses is the OBD,

  H_1: At least one dose is OBD admissible.

- We first consider type I error and then power.
- **Challenge**: H_0 consists of multiple hypotheses:

		d_1	d_2				d_1	d_2
$H_0(0,0)$	tox	$\phi_{T,0}$	$\phi_{T,0}$		$H_0(1,1)$	tox	$\phi_{T,1}$	$\phi_{T,0}$
	eff	$\phi_{E,1}$	$\phi_{E,1}$			eff	$\phi_{E,0}$	$\phi_{E,1}$
$H_0(0,1)$	tox	$\phi_{T,0}$	$\phi_{T,0}$		$H_0(1,2)$	tox	$\phi_{T,1}$	$\phi_{T,0}$
	eff	$\phi_{E,0}$	$\phi_{E,1}$			eff	$\phi_{E,0}$	$\phi_{E,0}$
$H_0(0,2)$	tox	$\phi_{T,0}$	$\phi_{T,0}$		$H_0(2,2)$	tox	$\phi_{T,1}$	$\phi_{T,1}$
	eff	$\phi_{E,0}$	$\phi_{E,0}$			eff	$\phi_{E,0}$	$\phi_{E,0}$

Global type I error

- H_0 consists of $K = \sum_{j=1}^{J+1} j$ hypotheses:

$$H_0(s,k): \underbrace{\pi_{T,1} = \pi_{T,2} = \cdots = \pi_{T,s} = \phi_{T,1}}_{\text{acceptable toxicity}} < \underbrace{\pi_{T,s+1} = \cdots = \pi_{T,k} = \pi_{T,k+1} = \cdots = \pi_{T,J} = \phi_{T,0}}_{\text{unacceptable toxicity}};$$

$$\underbrace{\pi_{E,1} = \pi_{E,2} = \cdots = \pi_{E,s} = \pi_{E,s+1} = \cdots = \pi_{E,k} = \phi_{E,0}}_{\text{unacceptable efficacy}} < \underbrace{\pi_{E,k+1} = \cdots = \pi_{E,J} = \phi_{E,1}}_{\text{acceptable efficacy}},$$

where $s, k \in \{0, 1, \ldots, J\}$ with $s \leq k$.

- Define ***global type I error*** to encompass all $H_0(s,k)$

$$\alpha = \Pr(reject\ H_0 | H_0) = \max_{(s,k)} \{\alpha(s,k)\}$$

where $\alpha(s,k) = \Pr(reject\ H_0 | H_0(s,k))$

Generalized power

- Similarly, H_1 encompasses a collection of $\sum_{j=1}^{J} j$ hypotheses

		d_1	d_2
$H_1(0,1)$	eff	$\phi_{E,1}$	$\phi_{E,1}$
	tox	$\phi_{T,1}$	$\phi_{T,0}$
$H_1(0,2)$	eff	$\phi_{E,1}$	$\phi_{E,1}$
	tox	$\phi_{T,1}$	$\phi_{T,1}$
$H_1(1,2)$	eff	$\phi_{E,0}$	$\phi_{E,1}$
	tox	$\phi_{T,1}$	$\phi_{T,1}$

$$H_1(u,v): \underbrace{\pi_{T,1}=\pi_{T,2}=\cdots=\pi_{T,u}=\pi_{T,u+1}=\cdots=\pi_{T,v}=\phi_{T,1}}_{\text{acceptable toxicity}} < \underbrace{\pi_{T,v+1}=\cdots=\pi_{T,J}=\phi_{T,0}}_{\text{unacceptable toxicity}};$$

$$\underbrace{\pi_{E,1}=\pi_{E,2}=\cdots=\pi_{E,u}=\phi_{E,0}}_{\text{unacceptable efficacy}} < \underbrace{\pi_{E,u+1}=\cdots=\pi_{E,v}=\pi_{E,v+1}=\cdots=\pi_{E,J}=\phi_{E,1}}_{\text{acceptable efficacy}},$$

Generalized power

- **Additional challenge**: the standard definition of power, i.e., $\Pr(reject\ H_0 | H_1(u,v))$, is not sufficient to characterize dose optimization.
- Example: d_1 is safe but futile and d_2 is safe and efficacious. The decision that only d_1 is OBD admissible leads to reject H_0, but is incorrect.
- It is important to account for the quality of the admissible dose selection!

Generalized power

- ***Generalized power I***

$$\beta_1(u,v) = \Pr(reject\ H_0\ \&\ all\ doses\ in\ A\ are\ truly\ safe\ and\ efficacious \mid H_1(u,v))$$

where *A* denotes the admissible dose set selected by the design.

- ***Generalized power II***

$$\beta_2(u,v) = \Pr(reject\ H_0\ \&\ at\ least\ one\ dose\ in\ A\ is\ truly\ safe\ and\ efficacious \mid H_1(u,v))$$

- Accordingly, define ***global power I and II*** to encompass all $H_1(u,v)$

$$\beta_i = min_{u,v}\{\beta_i(u,v)\} \quad \text{for } i = 1, 2.$$

Generalized power

- Both generalized powers are stricter than the standard power.
- The additional requirement is to ensure the quality of subsequent final OBD selection (i.e., step 2).
- Generalized power I is stricter than generalized power II.
- The choice of which power depends on the trial characteristics and the user's tolerability of false positives.
- Under the two-stage decision-making paradigm, a false positive is of less concern than standard hypothesis testing because the false positive (made in step 1) could be identified and corrected later in step 2 based on more data. Thus, generalized power II may be a good option when reducing the sample size is of top priority.

Least favorable set

Theorem 1. *Define the least favorable set* $\widetilde{H}_1 = \{H_1(j), j = 1, \cdots, J\}$, *where*

$$H_1(j) = \left(\begin{array}{ccc} \underbrace{\pi_{T,1} = \cdots = \pi_{T,j-1} = \phi_{T,1}}_{\text{safe but futile}} & \underbrace{\pi_{T,j} = \phi_{T,1}}_{\text{safe and efficacious}} & \underbrace{\pi_{T,j+1} = \cdots = \pi_{T,J} = \phi_{T,0}}_{\text{toxic and efficacious}} \\ \underbrace{\pi_{E,1} = \cdots = \pi_{E,j-1} = \phi_{E,0}} & \underbrace{\pi_{E,j} = \phi_{E,1}} & \underbrace{\pi_{E,j+1} = \cdots = \pi_{E,J} = \phi_{E,1}} \end{array} \right).$$

For any $H_1(u, v)$, *with* $u, v \in \{0, 1, 2, \ldots, J\}$ *and* $u < v$, *there exists an* $H_1(j)$ *such that* $\beta_i(j) \leq \beta_i(u, v)$, $i = 1, 2$, *where* $\beta_1(j)$ *and* $\beta_2(j)$ *denote the generalized power I and II under* $H_1(j)$, *respectively.*

- Thus, the global power can be simplified as

$$\beta_i = min_j \{ \beta_i(j) \} \text{ for } i = 1, 2, j = 1, \ldots, J$$

MERIT design

MERIT (Multiple-dosE RandomIzed phase II Trial) design

1. Specify target global type I error and power α^* and β^*;
2. Randomize $J \times n$ patients equally to J doses;
3. In any dose arm d_j, if $n_{E,j} \geq m_E$ and $n_{T,j} \leq m_T$, we reject H_0 and claim that d_j is OBD admissible, where m_E and m_T are decision boundaries.

*$n_{E,j}$ and $n_{T,j}$ are the total number of patients who experience efficacy and toxicity in dose arm d_j.

Calculation of α and β

- (n, m_E, m_T) are determined by numerical search such at the design controls the global type I error and global power at nominal values α^* and β^*
- Type I error

$$\begin{aligned}\alpha(s,k) &= \Pr(\text{reject } H_0(s,k) | H_0(s,k)) \\ &= 1 - \Big\{ \big(1 - \Pr(n_T \le m_T, n_E \ge m_E; n, \phi_{T,1}, \phi_{E,0})\big)^s \\ &\quad \times \big(1 - \Pr(n_T \le m_T, n_E \ge m_E; n, \phi_{T,0}, \phi_{E,0})\big)^{k-s} \\ &\quad \times \big(1 - \Pr(n_T \le m_T, n_E \ge m_E; n, \phi_{T,0}, \phi_{E,1})\big)^{J-k} \Big\}.\end{aligned}$$

- Power

$$\begin{aligned}\beta_1(j) = \Pr(&n_{E,1} < m_E, \ldots, n_{E,j-1} < m_E, n_{T,j+1} > m_T, \ldots, n_{T,j} > m_T, \\ &n_{E,j} \ge m_E, n_{T,j} \le m_T \,|H_1(j)),\end{aligned}$$

$$\beta_2(j) = \Pr(n_{E,j} \ge m_E, n_{T,j} \le m_T \,|H_1(j))$$

N and decision boundaries

- Sample size and decision boundaries of MERIT when $(\phi_{T,0}, \phi_{T,1}) = (0.4, 0.2)$ and $(\phi_{E,0}, \phi_{E,1}) = (0.2, 0.4)$.

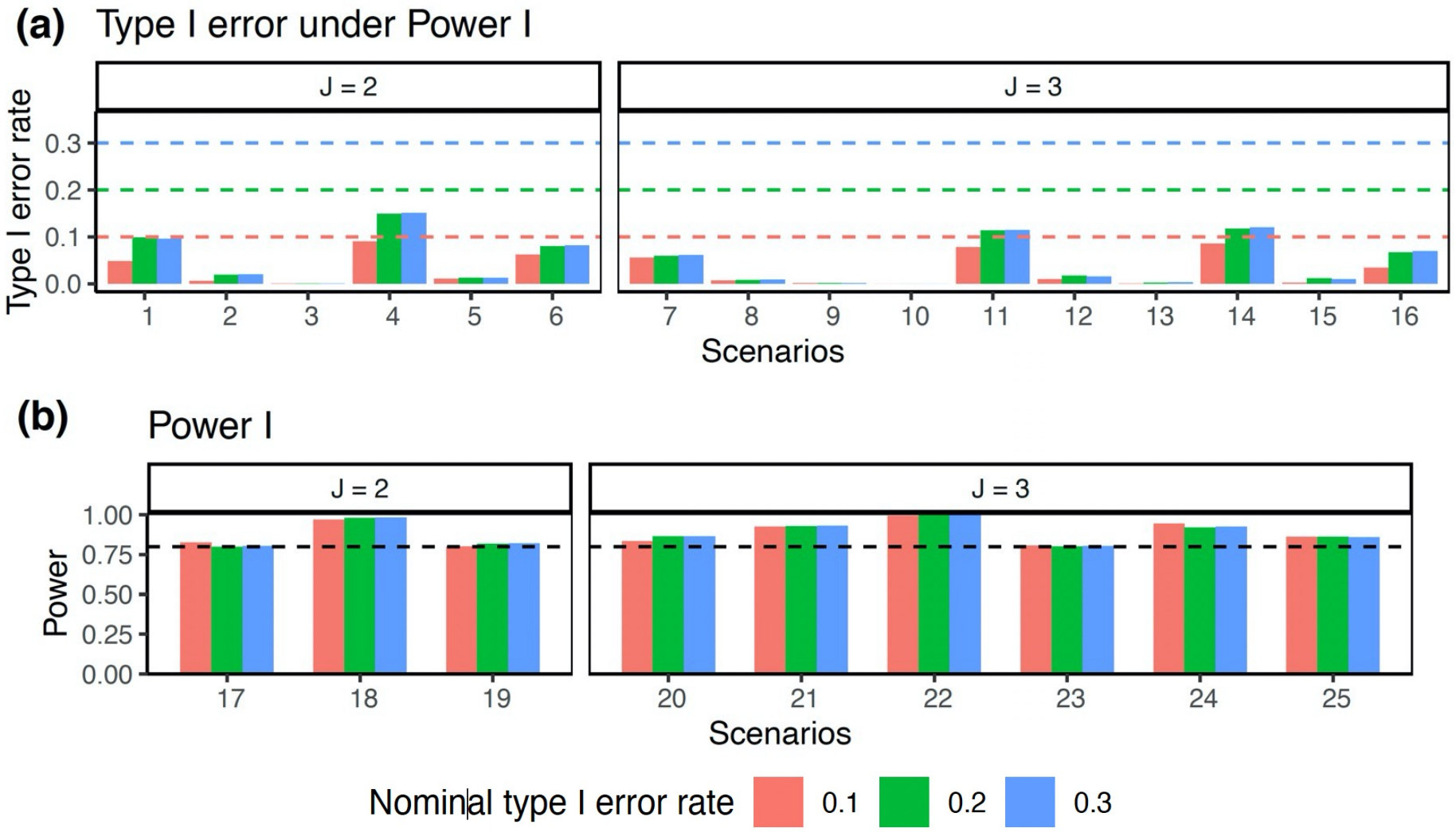
J	β^*	$\alpha^* = 0.1$			$\alpha^* = 0.2$			$\alpha^* = 0.3$		
		n	m_T	m_E	n	m_T	m_E	n	m_T	m_E
2	0.6	26	7	9	18	5	6	18	5	6
	0.7	34	9	11	25	7	8	20	6	6
	0.8	45	12	14	35	10	10	24	7	7
3	0.6	27	7	9	19	5	6	18	5	6
	0.7	36	10	12	26	7	8	23	7	7
	0.8	47	13	15	37	11	11	24	7	7

Practical consideration

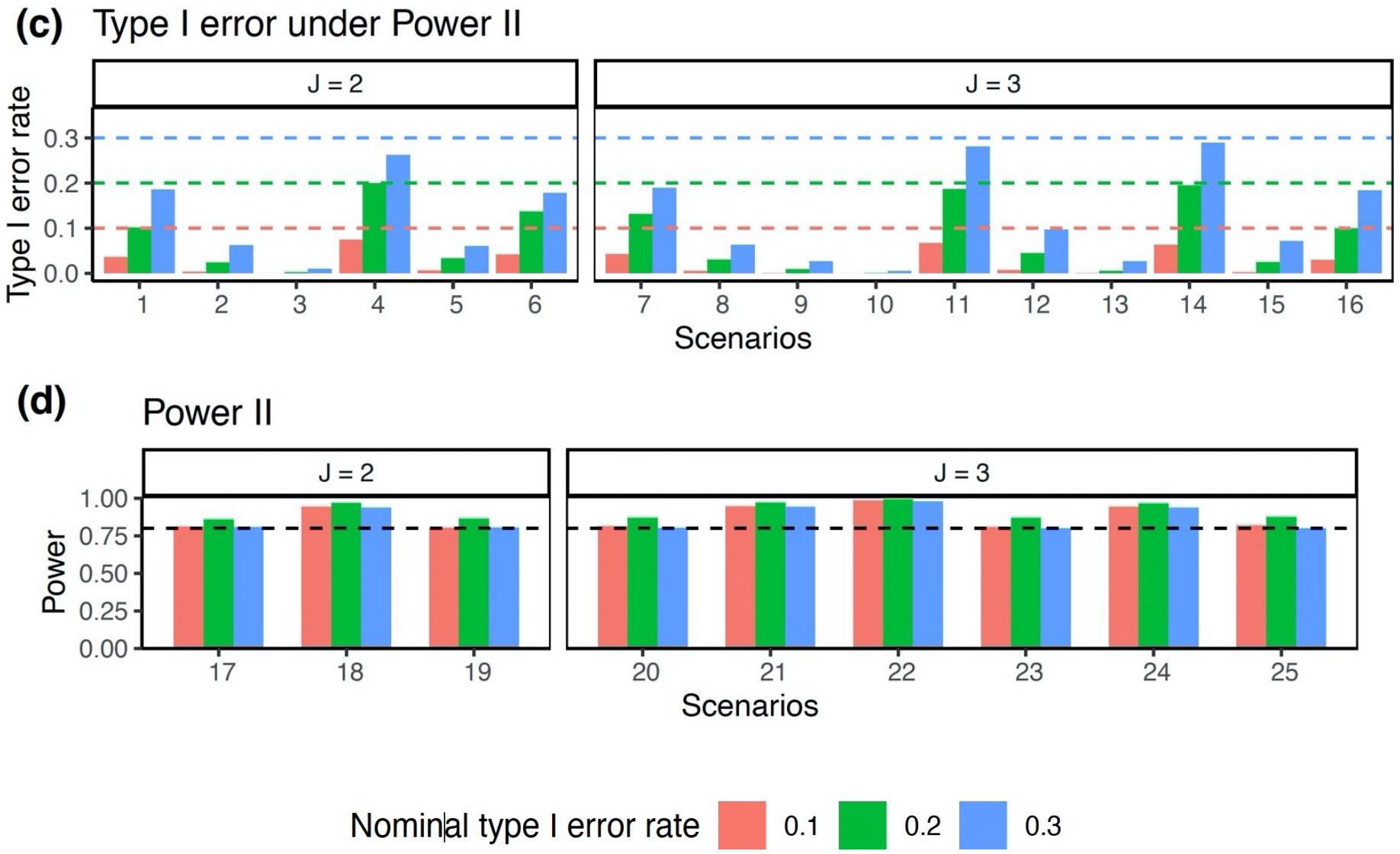
- In small samples, isotonic transformed $\{n_{T,j}\}$ and $\{n_{E,j}\}$ should be used to compare with boundaries (m_T, m_E) when the non-decreasing assumption is sound for toxicity and efficacy.
- In some trials, it may be desirable to add futility and safety interim monitoring:
  - Stop arm j for safety if $\Pr\left(\pi_{T,j} > \phi_{T,1} \middle| data\right) > C_T$,
  - Stop arm j for futility if $\Pr\left(\pi_{E,j} < \phi_{E,1} \middle| data\right) > C_E$, where C_T and C_E are probability cutoffs (e.g., 0.95).
- Whether to include interim monitoring depends on the availability of Y_T and Y_E, logistics, and other considerations. Typically, 1 or 2 interims are sufficient.

Simulation

- Type I error and power of MERIT when $(\phi_{T,0}, \phi_{T,1}) = (0.4, 0.2)$ and $(\phi_{E,0}, \phi_{E,1}) = (0.2, 0.4)$.

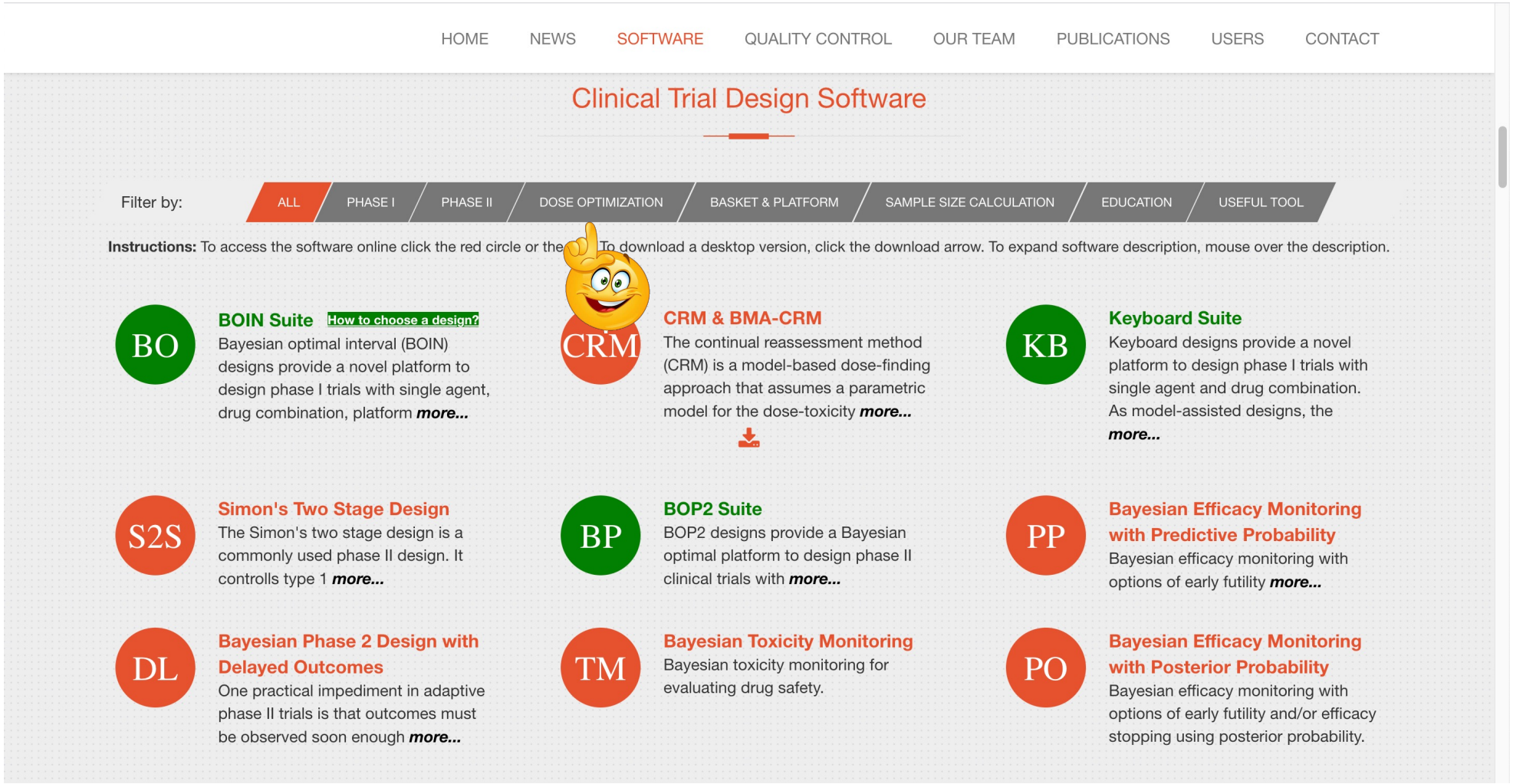


Simulation


(c) Type I error under Power II
J = 2
J = 3
Type I error rate
0.0
0.1
0.2
0.3
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
Scenarios
(d) Power II
J = 2
J = 3
Power
0.00
0.25
0.50
0.75
1.00
17
18
19
20
21
22
23
24
25
Scenarios
Nominal type I error rate
0.1
0.2
0.3

www.trialdesign.org

www.trialdesign.org



www.trialdesign.org

HOME NEWS SOFTWARE QUALITY CONTROL OUR TEAM PUBLICATIONS USERS CONTACT

Clinical Trial Design Software

Filter by: ALL | PHASE I | PHASE II | DOSE OPTIMIZATION | BASKET & PLATFORM | SAMPLE SIZE CALCULATION | EDUCATION | USEFUL TOOL

Instructions: To access the software online click the red circle or the title. To download a desktop version, click the download arrow. To expand software description, mouse over the description.

BOIN12: to find optimal biological dose for targeted and immune therapies
BOIN12 is a simple and flexible Bayesian optimal interval ***more...***

TITE-BOIN12: extension of BOIN12 for late-onset toxicity and efficacy
+ is an extension of BOIN12 to accommodate ***more...***

U-BOIN: a 2-stage design to find optimal biological dose for targeted and immune therapies
U-BOIN is a utility-based seamless Bayesian phase I/II trial ***more...***

ISO

Isotonic regression design to find optimal biological dose
This design is used to find the optimal biological dose (OBD) for molecularly targeted agents and ***more...***

MER

MERIT: multiple-dose Randomized Phase II Trial Design for Dose Optimization and Sample Size Determination
A simple, rigorous and ***more...***

DROID: dose-ranging approach to optimizing dose in oncology drug development
A new dose-ranging approach to oncology dose optimization. ***more...***

www.trialdesign.org

HOME SOFTWARE OUR TEAM PUBLICATIONS CONTACT

MERIT: Multiple-dose Randomized Phase II Trial Design for Dose Optimization and Sample Size Determination

PID: 1126; Version: V1.1.0.0 ; Last Updated: 2/18/2023

Peng Yang and Ying Yuan

Department of Biostatistics, The University of Texas MD Anderson Cancer Center

Trial Setting | Operating Characteristics | Trial Conduct | Reference

Number of Doses:

◉ 2 ○ 3 ○ 4

Toxicity Rates:

Null $\phi_{T,0}$: 0.4

Alternative $\phi_{T,1}$: 0.2

Efficacy Rates:

Null $\phi_{E,0}$: 0.2

Alternative $\phi_{E,1}$: 0.4

MERIT Design

www.trialdesign.org

HOME SOFTWARE OUR TEAM PUBLICATIONS CONTACT

Global Type I Error Rate:

0.2

Generalized Power:

Power I Power II

0.8

Inlucde toxicity and futility monitoring

Setting to Optimize the Design:

Correlation between toxicity and efficacy

positive negative

Correlation

0 0.5 1

0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1

Number of simulations

5000

Seeds of the random number generator

123

Calculate Optimal Design

www.trialdesign.org

MERIT: Multiple-dose Randomized Phase II Trial Design for Dose Optimization and Sample Size Determination

PID: 1126; Version: V1.1.0.0 ; Last Updated: 2/18/2023

Peng Yang and Ying Yuan

Department of Biostatistics, The University of Texas MD Anderson Cancer Center

Trial Setting | Operating Characteristics | Trial Conduct | Reference

Number of Doses:

(•) 2 ( ) 3 ( ) 4

Toxicity Rates:

Null $\phi_{T,0}$: 0.4

Alternative $\phi_{T,1}$: 0.2

Efficacy Rates:

Null $\phi_{E,0}$: 0.2

Alternative $\phi_{E,1}$: 0.4

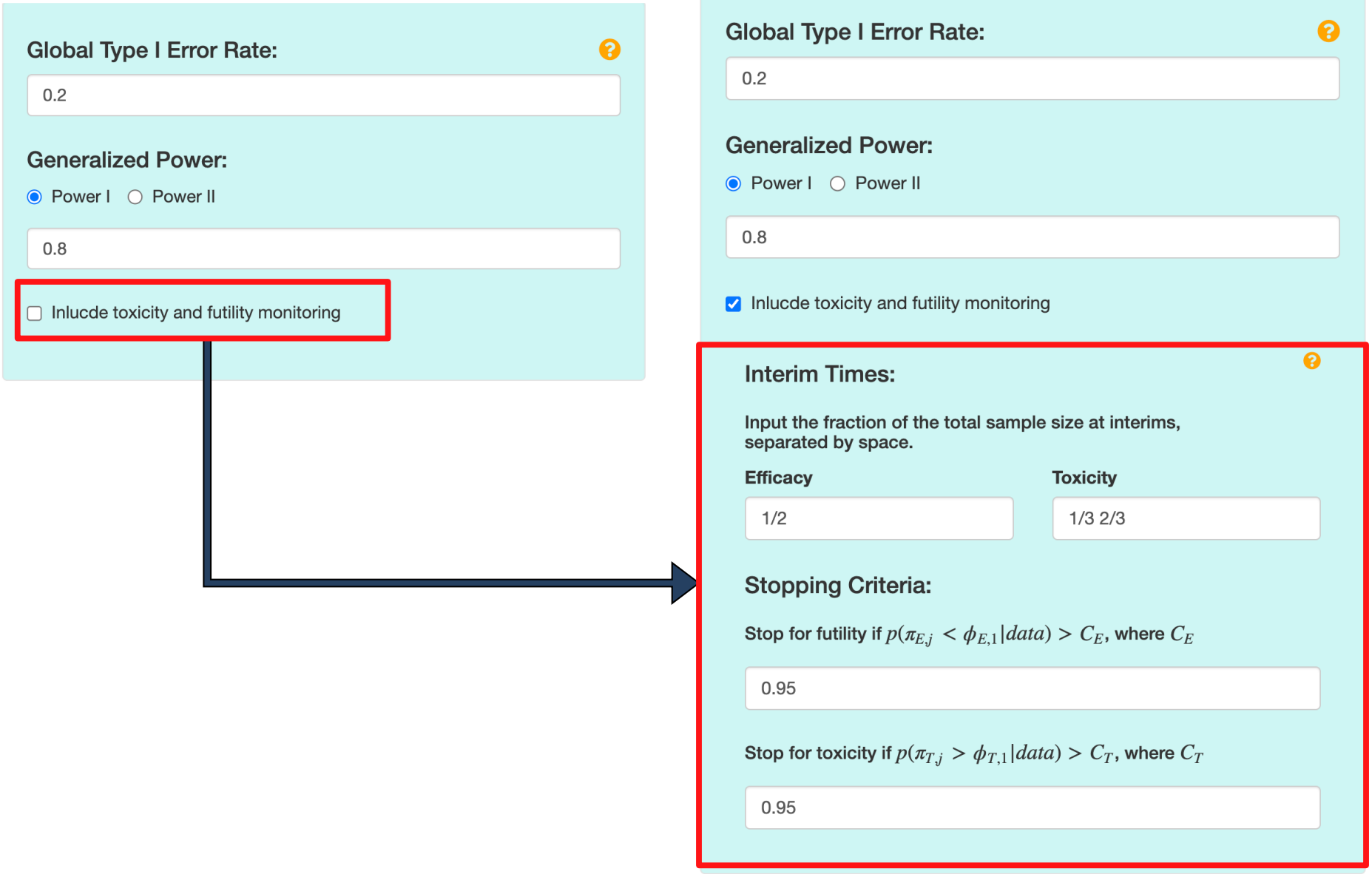
MERIT Design

Download MERIT Design

Design Description

In this trial, the toxicity rates of 0.4 and 0.2 are considered unacceptable and acceptable, respectively, while the efficacy rates of 0.2 and 0.4 are considered unacceptable and acceptable, respectively. In order to control the global Type I error rate at 0.2 and achieve a global generalized power I of 0.8, a minimum sample size of 44 per arm is required. The generalized power I is defined as the probability of rejecting the null hypothesis that none of the doses are considered optimal biological doses (OBD) admissible and all doses identified as OBD admissible are truly safe and efficacious given the alternative hypothesis that at least one dose is OBD admissible. At the end of the trial, perform isotonic regression on toxicity and efficacy data across all doses. A dose will be considered OBD admissible if the isotonically transformed number of toxicity <= 13 and the isotonically transformed number of efficacy >= 13.

www.trialdesign.org



www.trialdesign.org

Number of Doses:

(•) 2 ( ) 3 ( ) 4

Toxicity Rates:

Null $\phi_{T,0}$: 0.4

Alternative $\phi_{T,1}$: 0.2

Efficacy Rates:

Null $\phi_{E,0}$: 0.2

Alternative $\phi_{E,1}$: 0.4

Global Type I Error Rate: 0.2

Generalized Power:

(•) Power I ( ) Power II

0.8

[x] Inlucde toxicity and futility monitoring

Interim Times:

MERIT Design

Download MERIT Design

Design Description

In this trial, the toxicity rates of 0.4 and 0.2 are considered unacceptable and acceptable, respectively, while the efficacy rates of 0.2 and 0.4 are considered unacceptable and acceptable, respectively. In order to control the global Type I error rate at 0.2 and achieve a global generalized power I of 0.8, a minimum sample size of 45 per arm is required. The generalized power I is defined as the probability of rejecting the null hypothesis that none of the doses are considered optimal biological doses (OBD) admissible and all doses identified as OBD admissible are truly safe and efficacious given the alternative hypothesis that at least one dose is OBD admissible. At the end of the trial, perform isotonic regression on toxicity and efficacy data across all doses. A dose will be considered OBD admissible if the isotonically transformed number of toxicity <= 13 and the isotonically transformed number of efficacy >= 13.
During the trial, the toxicity and efficacy of each dose arm will be monitored independently using the stopping criteria outlined in Table 1. If the isotonically transformed toxicity and efficacy acrosss topping boundaries, enrollment in that particular dose arm will be suspended.

Table 1. Stopping boundaries for toxicity and efficacy.

CSV | Excel | PDF | Print | Search:

# of patients treated	Stop if # toxicity >=	Stop if # efficacy <=
15	6	NA
23	NA	5
30	10	NA

Showing 1 to 3 of 3 entries Previous 1 Next

Note: 'NA' means that this endpoint will not be used to make go/no-go decision at the interim

www.trialdesign.org

MERIT: Multiple-dose Randomized Phase II Trial Design for Dose Optimization and Sample Size Determination

PID: 1126; Version: V1.1.0.0 ; Last Updated: 2/18/2023

Peng Yang and Ying Yuan

Department of Biostatistics, The University of Texas MD Anderson Cancer Center

Trial Setting | Operating Characteristics | Trial Conduct | Reference

Enter Simulation Scenarios:

Add a scenario | Remove a scenario | Save scenarios

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

	Tox(d1)	Eff(d1)	Tox(d2)	Eff(d2)
Scenario 1	0.40	0.40	0.40	0.40
Scenario 2	0.40	0.20	0.40	0.20
Scenario 3	0.20	0.20	0.20	0.20
Scenario 4	0.20	0.40	0.40	0.40
Scenario 5	0.20	0.40	0.20	0.40
Scenario 6	0.20	0.20	0.20	0.40

Number of simulations: 5000

Set seed: 123

Run Simulation

Operating Characteristics

www.trialdesign.org

Operating Characteristics

Copy CSV Excel Print

Search:

Scenarios	Metrics	Values	Average sample size
1	Type I error	0.093	44
2	Type I error	0.001	44
3	Type I error	0.082	44
4	Power	0.801	44
5	Power	0.982	44
6	Power	0.815	44

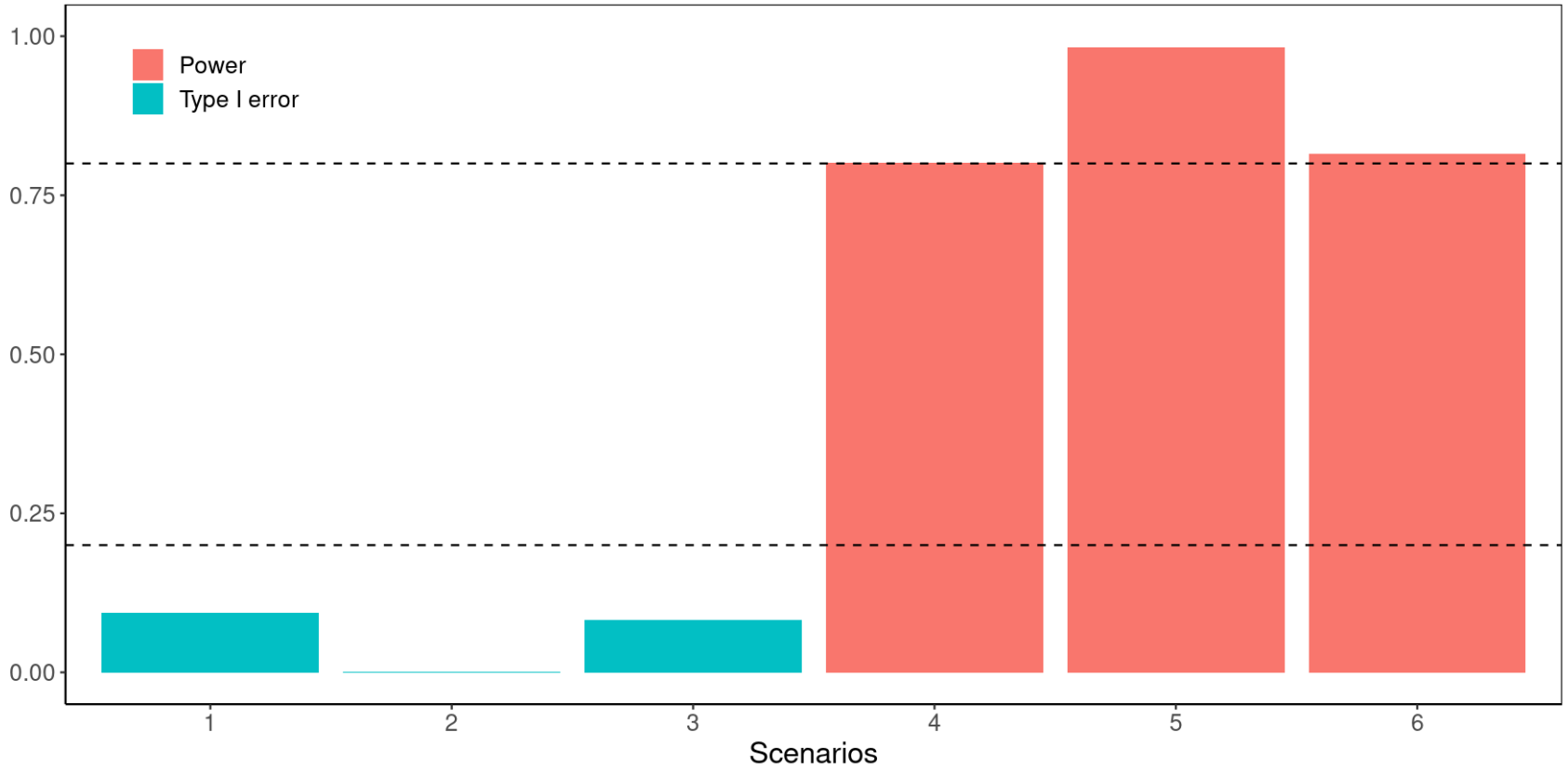
Showing 1 to 6 of 6 entries

Previous 1 Next

www.trialdesign.org

Download Figure 1

Figure 1. Type I error and power of MERIT design when unacceptable and acceptable toxicity rates are 0.4 and 0.2, and unacceptable and acceptable efficacy rates are 0.2 and 0.4. The horizontal dashed lines represent the nominal values of type I error (0.2) and power I (0.8).



Discussion

- Adaptive randomization is not particularly helpful here.
  - Requires real-time efficacy readout and a more complicated randomization system, and introduce higher variation and potential biased estimates.
  - Equal randomization with 1 or 2 interim monitoring is often sufficient for small sample sizes.
- MERIT can be used with any phase I MTD-finding designs (e.g., CRM/BOIN) or OBD-finding designs (e.g., BOIN12).
- MERIT can used to construct phase II/III designs.
- Continuous and survival endpoints are topics of ongoing research.

References

- Yang, P., Li, D., Lin, R., Huang, Bo., & Yuan, Y. (2023). Design and Sample Size Determination for Multiple-dose Randomized Phase II Trials for Dose Optimization. https://arxiv.org/abs/2302.09612
- Lin R, Zhou Y, Yan F, Li D, Yuan Y. BOIN12 (2020) Bayesian Optimal Interval Phase I/II Trial Design for Utility-Based Dose Finding in Immunotherapy and Targeted Therapies. JCO Precis Oncol., 4:PO.20.00257. doi: 10.1200/PO.20.00257.
- Zhou Y, Lin R, Lee JJ, Li D, Wang L, Li R, Yuan Y. (2022) TITE-BOIN12: A Bayesian phase I/II trial design to find the optimal biological dose with late-onset toxicity and efficacy. Stat Med., 41(11):1918-1931.
- Jiang, L., Yuan, Y. (2022) Seamless Phase 2-3 Design: A Useful Strategy to Reduce the Sample Size for Dose Optimization, https://doi.org/10.48550/arXiv.2211.02046


Thank You!