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

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Manuscript Software

Introduction

- In 2022, **FDA** initiated **Project Optimus** "to reform the dose optimization and dose selection paradigm in oncology drug development."
- Paradigm shifting from maximum tolerated dose (MTD) to optimal biological dose (OBD).

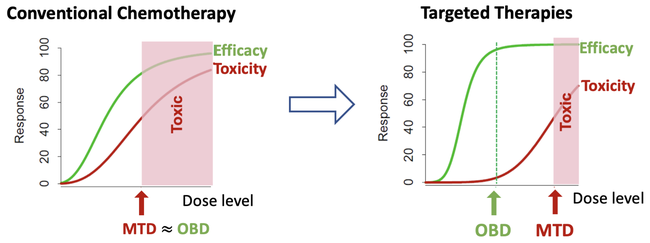


Figure 1. Paradigm shifting for dose optimization.

- MTD-based dose finding was often appropriate to inform RP2D;
- Safety alone is not sufficient to inform optimal RP2D.

Design a trial to compare multiple dosages (FDA, 2023)

⇒ two-stage decision-making paradigm

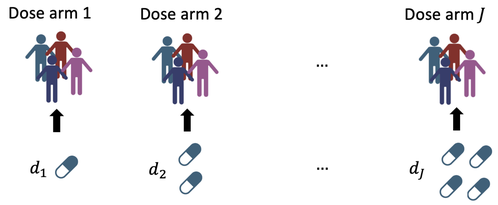
1 Determination of OBD admissible dose set
- The objective is to identify a dose set (i.e., OBD admissible set $\mathcal{A}$) that satisfies certain **safety** and **efficacy** requirements in a statistical manner (e.g. type I error and power).

2 Identification of the OBD
- The OBD will be selected from $\mathcal{A}$ based on the totality of activity, safety, and tolerability data empirically.

Statistical Modelling

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 application, $J = 2$ or 3, and d_J is often the MTD or maximum administered dose.



- Let Y_T and Y_E denote the binary toxicity and efficacy endpoints, respectively.
- Let $\pi_{T,j} = \Pr(Y_T = 1|d_j)$ and $\pi_{E,j} = \Pr(Y_E = 1|d_j)$ denotes the probability of the occurrence of toxicity and efficacy events.

- For toxicity endpoint, we assume
  - $\phi_{T,0}$: the **null** toxicity rate that is **high** and deemed **unacceptable**;
  - $\phi_{T,1}$: the **alternative** toxicity rate that is **low** and deemed **acceptable**;
- For efficacy endpoint, we assume
  - $\phi_{E,0}$: the **null** efficacy rate that is **low** and deemed **unacceptable**;
  - $\phi_{E,1}$: the **alternative** efficacy rate that is **high** and deemed **acceptable**.

OBD admissible

$\pi_{T,j}$ / $\pi_{E,j}$	$\phi_{T,0}$	$\phi_{T,1}$
$\phi_{E,0}$	✗	✗
$\phi_{E,1}$	✗	✓

Global Type I Error

Consider H_0: none of the doses is the OBD.

- **Challenge:** consists of multiple hypotheses ($\sum_{j=1}^{J+1} j$).

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

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

where $s, k \in \{0, 1, \ldots, J\}$ and $s \le k$.

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

Define global type I error that encompasses all $H_0(s,k)$ as follows:

$$\alpha = \Pr(\text{reject } H_0 | H_0) = \max_{0 \le s \le J,\ s \le k \le J} \{\alpha(s,k)\}, \quad (1)$$

where $\alpha(s,k) = \Pr(\text{Reject } H_0(s,k) | H_0(s,k))$.

Global Generalized Powers

Consider H_1: at least one dose is the OBD admissible.

- **Challenge**: consists of multiple hypotheses ($\sum_{j=1}^{J} j$).

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

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

where $u, v \in \{0, 1, \ldots, J\}$ and $u < v$.

		d_1	d_2
$H_1(0,1)$	Tox	$\phi_{T,1}$	$\phi_{T,0}$
	Eff	$\phi_{E,1}$	$\phi_{E,1}$
Selection		✓	✓
		✓	✓

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

: OBD admissible

- **Additional challenge**: the standard definition of power, which rejects the H_0, is not sufficient to account for the characteristics of dose optimization.
- Generalized power I:

  $\beta_1(u,v) =$ Pr(reject H_0 and all doses in $\mathcal{A}$ are truly safe and efficacious $| H_1(u,v)$)
- Generalized power II:

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

Define global power I and power II that encompasses all $H_1(u,v)$ as follows:

$$\beta_i = \min_{u,v \in \{0,\cdots,J\}, u<v} \beta_i(u,v), \text{ for } i = 1, 2. \quad (2)$$

- Both generalized powers are stricter than the standard power.
- The choice of power depends on the characteristics of the trial and the user's tolerability of false positives.
- Power II is 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

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

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 $\beta_i(j) \le \beta_i(u,v)$, $i = 1, 2$, where $\beta_1(j)$ and $\beta_2(j)$ denote the generalized power I and II under $H_1(j)$, respectively. The global power in (2) can be equivalently defined as

$$\beta_i = \min_{j \in \{1,\ldots,J\}} \beta_i(j) \text{ for } i = 1, 2. \quad (3)$$

MERIT (Multiple-dosE RandomIzed Phase-II Trial) Design

- Specify target global type I error and power α^* and β^*;
- Randomize $J \times n$ patients equally to J doses;
- In any dose arm d_j, if $n_{E,j} \ge m_E$ and $n_{T,j} \le m_T$, we reject H_0 and claim that d_j is OBD admissible, where m_E and m_T are decision boundaries for efficacy and toxicity, respectively.
  * $n_{E,j}$ and $n_{T,j}$ are the total number of patients who experience efficacy and toxicity events in dose arm d_j.

Optimal Design Parameters

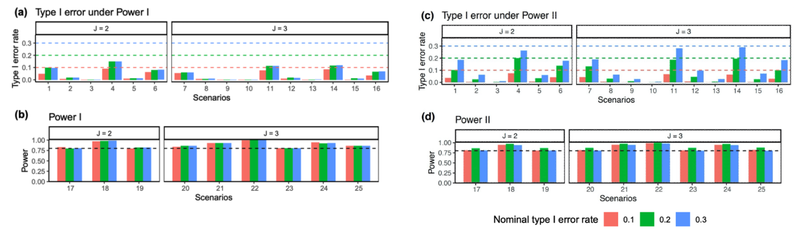
The **optimal design parameters** (n, m_T, m_E) are determined to **minimize sample size** n through numerical search such that the design controls the global type I error (1) and power (3) at nominal values α^* and β^*.

- Optimal design parameters (n, m_T, m_E) of MERIT design, when $J = 2$, $(\phi_{T,0}, \phi_{T,1}) = (0.4, 0.2)$, and $(\phi_{E,0}, \phi_{E,1}) = (0.2, 0.4)$.

β^*	β_1						β_2					
	$\alpha^* = 0.1$			$\alpha^* = 0.2$			$\alpha^* = 0.1$			$\alpha^* = 0.2$		
	n	m_T	m_E	n	m_T	m_E	n	m_T	m_E	n	m_T	m_E
0.6	26	7	6	23	6	26	25	6	5	18	5	4
0.7	33	9	7	30	8	33	33	8	6	24	7	5
0.8	44	12	8	39	11	44	39	11	8	30	8	5

Operating Characteristics

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



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