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MD Anderson Cancer Center

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# Bayesian Optimal Interval Design for Phase I Clinical Trials

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# Phase I oncology trials

- The goal of phase I oncology clinical trials is to find the maximum tolerated dose (MTD) with a target toxicity rate of $\phi$.
- The “3+3" design is the most commonly used design. Simple but poor performance.
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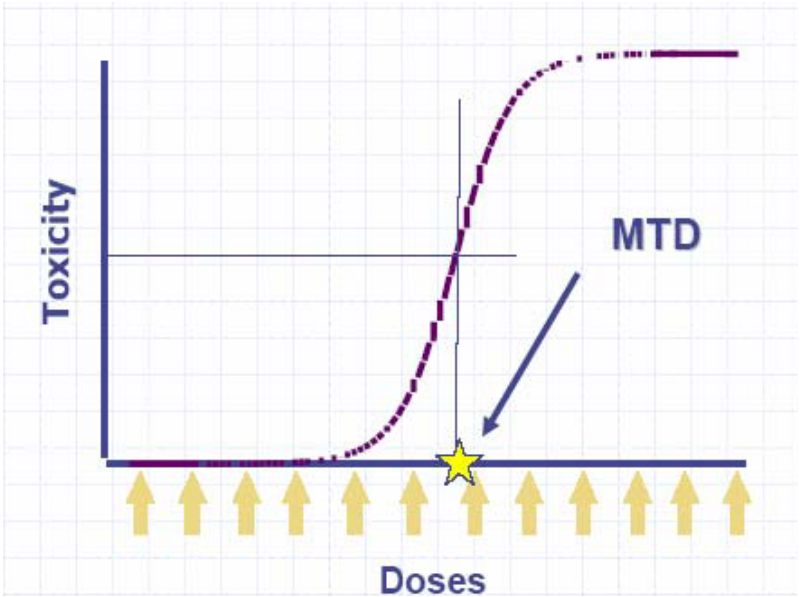

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  4. Superior operating characteristics $\longrightarrow$ comparable or better than commonly used designs

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Three possible decisions:

1. Escalation
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- Phase I trials can be viewed as a sequence of decision-making steps of dose assignment for patients who are sequentially enrolled into the trial

# In the real world

- In reality, the dose assignment is more complicated because $p_j$ is unknown
- We have to estimate $p_j$ based the observed data and make the decision
  - For example, the observed toxicity rate $\hat{p}_j = m_j/n_j$, where $m_j$ is the number of patients experienced toxicity at dose $j$, and $n_j$ is the number of patients treated at those $j$
- The decision is often incorrect because of small sample size and estimation uncertainty
  - e.g., escalate/deescalate when the current dose is above/below the MTD

# Motivation

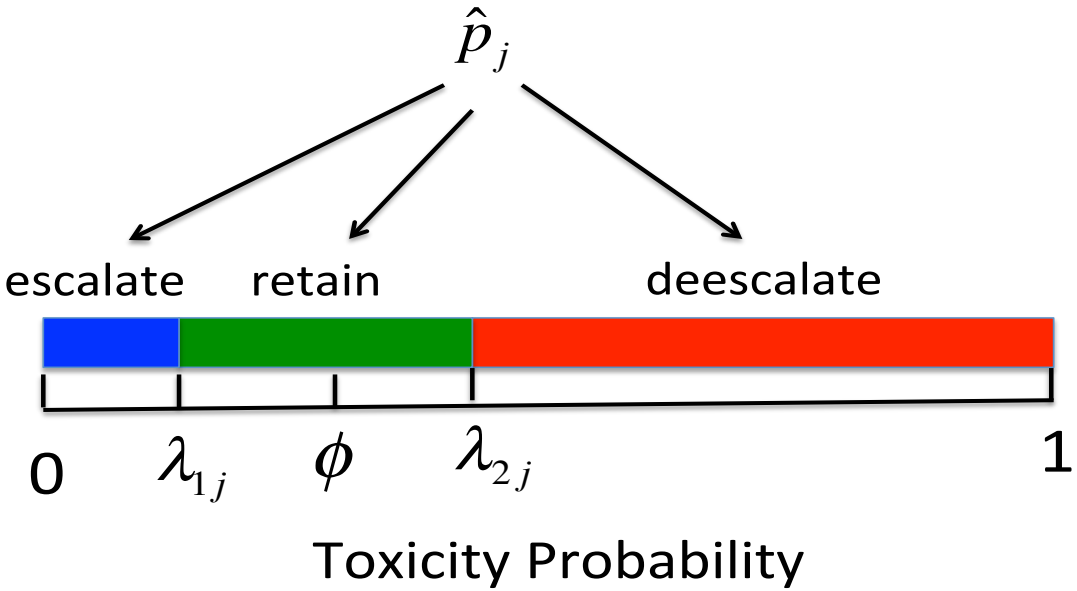
- From practical point of view, it is highly desirable to minimize such incorrect decisions and get as close as possible to the ideal case, in order to ensure each patient's treatment benefit.
- This motivates our trial design.

# The optimal interval design

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

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

# The optimal interval design



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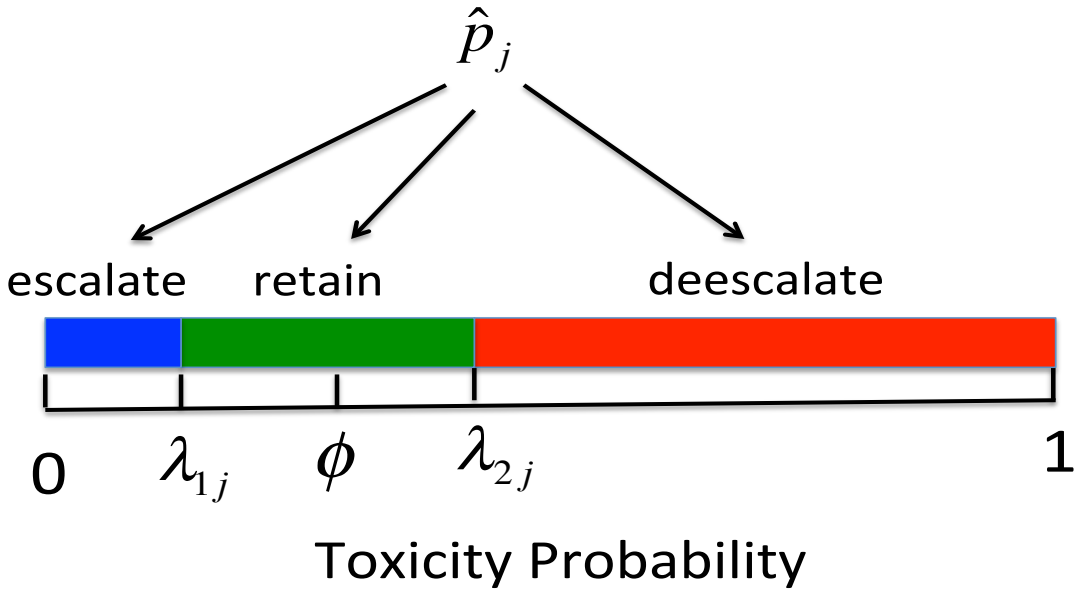


- The key issue is how to select the interval boundaries $\lambda_{1j}$ and $\lambda_{2j}$ to minimize the decision error of dose assignment.

# Notations and Setup

- Specify three point hypotheses

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

- $\phi_1$ is the highest toxicity probability that is deemed subtherapeutic (i.e., below the MTD) such that dose escalation should be made
- $\phi_2$ 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 $\phi_2 = 0.4$

# 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.

# 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 $\phi$ (or $H_0$), under which we want to minimize the average decision error rate for the trial conduct.
- This approach is analogous to sample size determination and power calculation.

# Remarks on the hypotheses

- In practice, we should avoid setting $\phi_1$ and $\phi_2$ at values very close to $\phi$ 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.
- Based on our experience, $\phi_1 \in [0.5\phi, 0.7\phi]$ and $\phi_2 \in [1.3\phi, 1.5\phi]$ are reasonable
- 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 $\phi_2 = 0.35$.

# Decision error rate

- Under the Bayesian paradigm, we assign each of the hypotheses a prior probability $\text{pr}(H_k), k = 0, \cdots, 2$.
- The probability of making an incorrect decision (or decision error rate) at each of the dose assignments is given by

$$\begin{aligned} \alpha &\equiv \text{pr}(\text{incorrect decision}) \\ &= \text{pr}(H_0)\text{pr}(\bar{\mathcal{R}}|H_0) \end{aligned}$$

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

# Optimal interval boundaries

- Assuming $\text{pr}(H_0) = \text{pr}(H_1) = \text{pr}(H_2) = 1/3$, i.e., *a priori* the current dose is equally likely to be below, above or equal to the MTD.
- The decision error rate is minimized when

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

# Interpretations of $\lambda_{1j}$ and $\lambda_{2j}$

## Theorem 1

- $\lambda_{1j}$ is the boundary at which the posterior probability of $H_1$ becomes more likely than that of $H_0$, i.e., $\lambda_{1j} = \text{argmax}_{\hat{p}_j}(\text{pr}(H_1|n_j, m_j) > \text{pr}(H_0|n_j, m_j))$;
- $\lambda_{2j}$ is the boundary at which the posterior probability of $H_2$ becomes more likely than that of $H_0$, i.e., $\lambda_{2j} = \text{argmin}_{\hat{p}_j}(\text{pr}(H_2|n_j, m_j) > \text{pr}(H_0|n_j, m_j))$.

- This provides intuitive justifications for the proposed dose escalation/deesclation rule!

# Optimal interval boundaries

- The dose escalation/deescalation boundaries are independent of $n_j$ and $j$ (when the noninformative prior is used) !!

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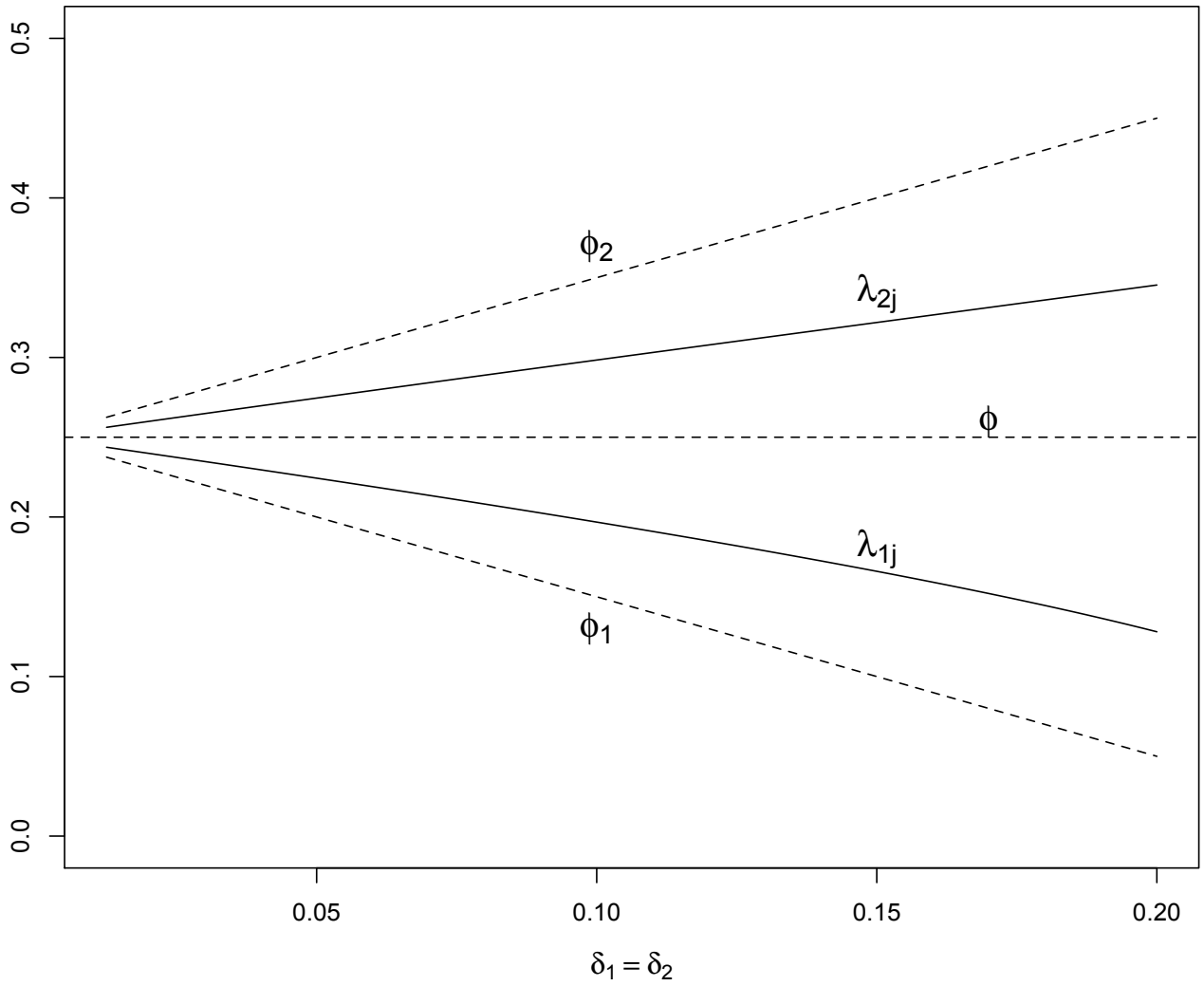
- Very appealing in practice because the same set of boundaries can be used throughout of the trial, no matter how many patients have been treated thus far and which level the current dose is.

# Optimal interval boundaries

Table : The values of $\lambda_{1j}$ and $\lambda_{2j}$ under the optimal interval design for different target toxicity rates .

| Interval boundaries | Target toxicity rate $\phi$ | | | | | |
|---|---|---|---|---|---|---|
| | 0.15 | 0.2 | 0.25 | 0.3 | 0.35 | 0.4 |
| $\lambda_{1j}$ | 0.118 | 0.157 | 0.197 | 0.236 | 0.276 | 0.316 |
| $\lambda_{2j}$ | 0.179 | 0.238 | 0.298 | 0.358 | 0.419 | 0.479 |

# Optimal interval boundaries



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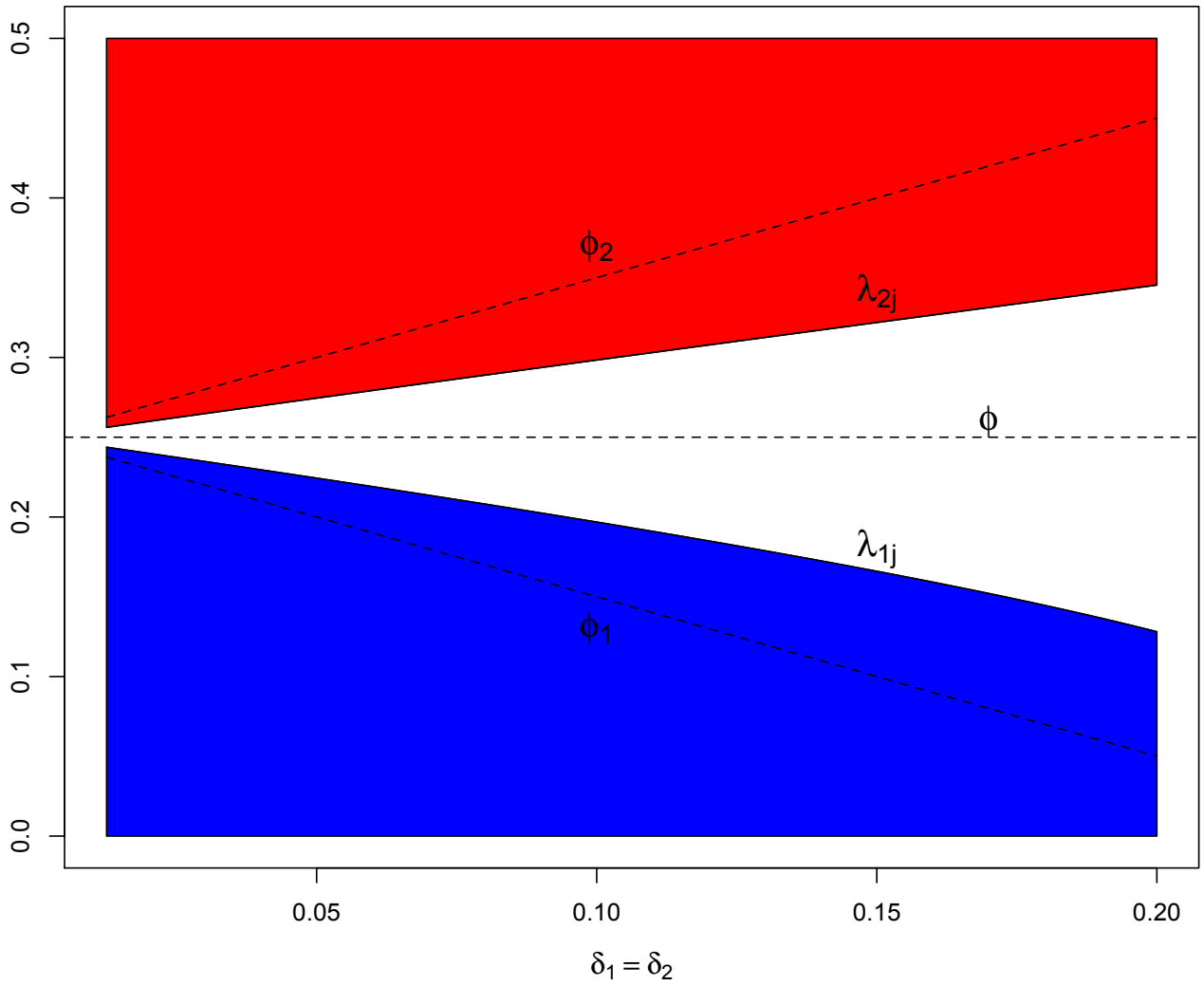

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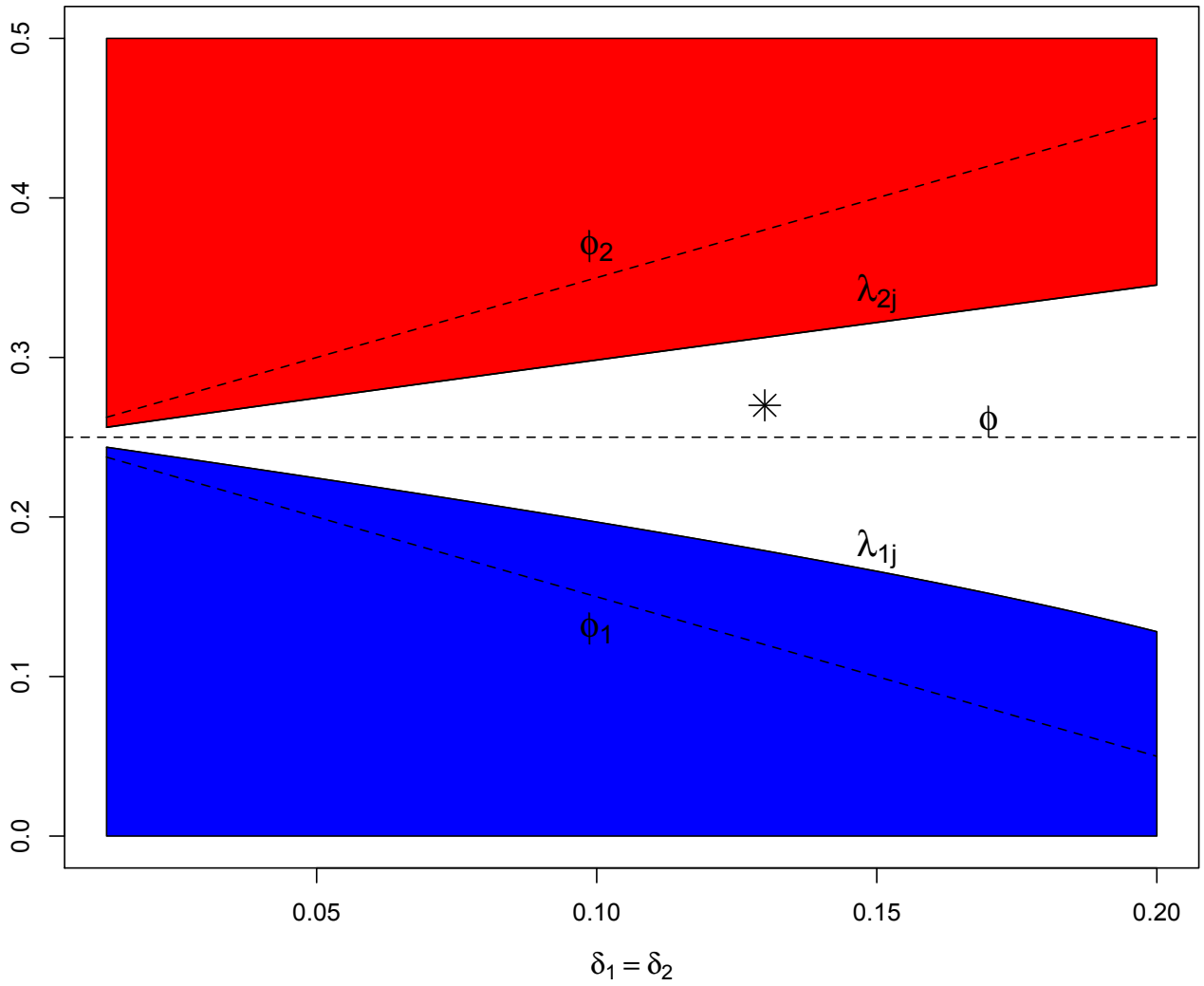

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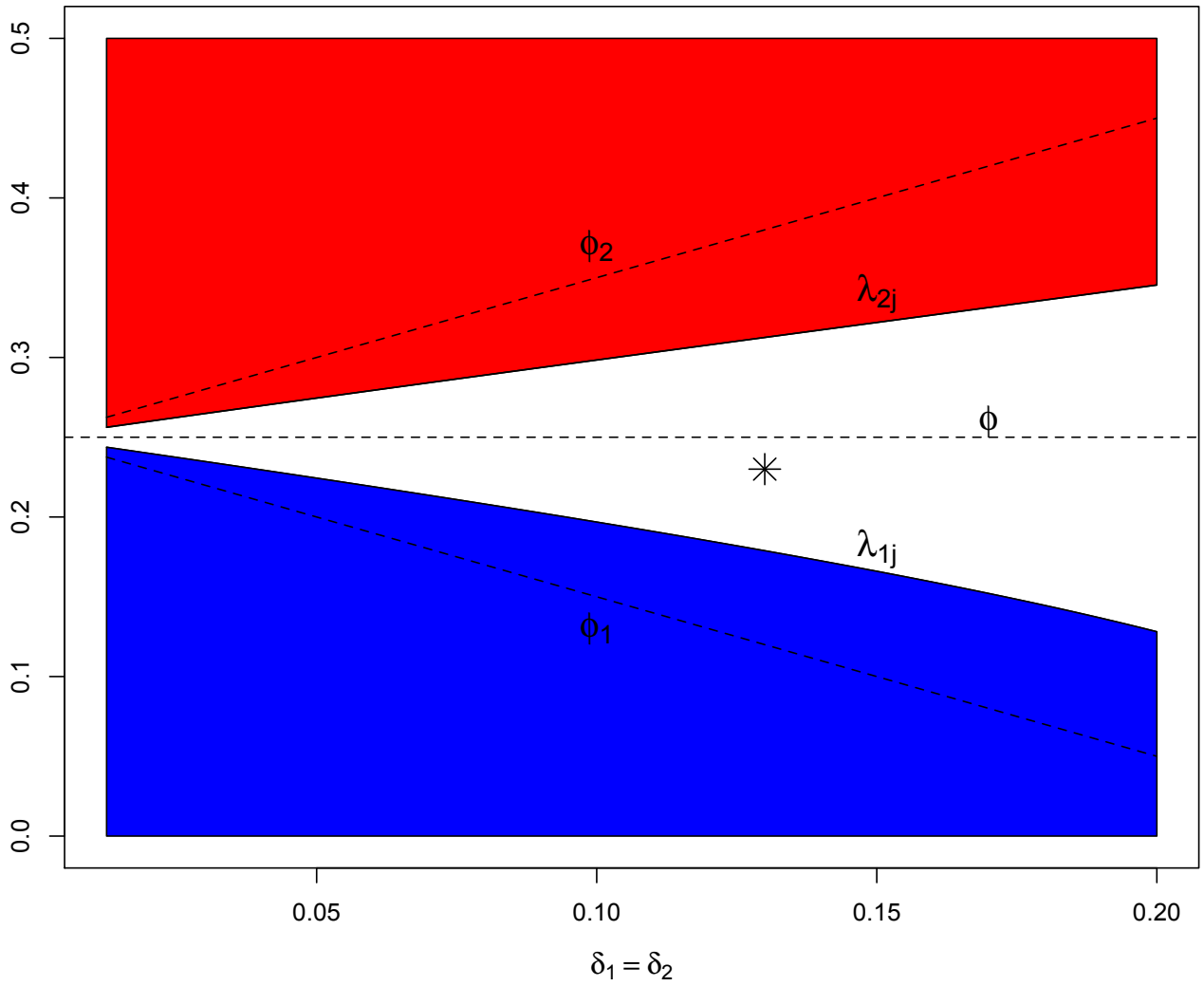


# Finite-sample property: coherence

**Theorem 2**

The proposed optimal interval design is (long-memory) coherent in the sense that the probability of dose escalation (or deescalation) is zero when the observed toxicity rate $\hat{p}_j$ at the current dose is higher (or lower) than the target toxicity rate $\phi$.

# Large-sample property: convergence

## Theorem 3

- Dose allocation in the optimal interval design converges almost surely to dose level $j^*$ if $p_{j^*} \in (\lambda_1, \lambda_2)$ and dose level $j^*$ is the only dose satisfying $p_{j^*} \in [\lambda_1, \lambda_2]$.
- If no dose level satisfies $p_j \in (\lambda_1, \lambda_2)$ but $\phi \in [p_1, p_J]$, the optimal interval design would eventually oscillate almost surely between the two dose levels at which the associated toxicity probabilities straddle the target interval.
- If there are multiple dose levels satisfying $p_j \in (\lambda_1, \lambda_2)$, the optimal interval design will converge almost surely to one of these levels.

# Selection of the MTD

- At the end of the trial, based on all observed data, we select as the MTD dose $j^*$, whose isotonic estimate of toxicity rate $\tilde{p}_{j^*}$ is closest to $\phi$;
- If there are ties for $\tilde{p}_{j^*}$, we select from the ties the highest dose level when $\tilde{p}_{j^*} < \phi$ and the lowest dose level when $\tilde{p}_{j^*} > \phi$.
- Under the proposed optimal dose assignment, we tend to treat patients at (or close to) the MTD, thus the design leads to a high probability of selecting the MTD because most data and statistical power are concentrated around the MTD.

# Safety stopping

- For patient safety, we impose the following dose elimination rule when implementing the optimal interval design.

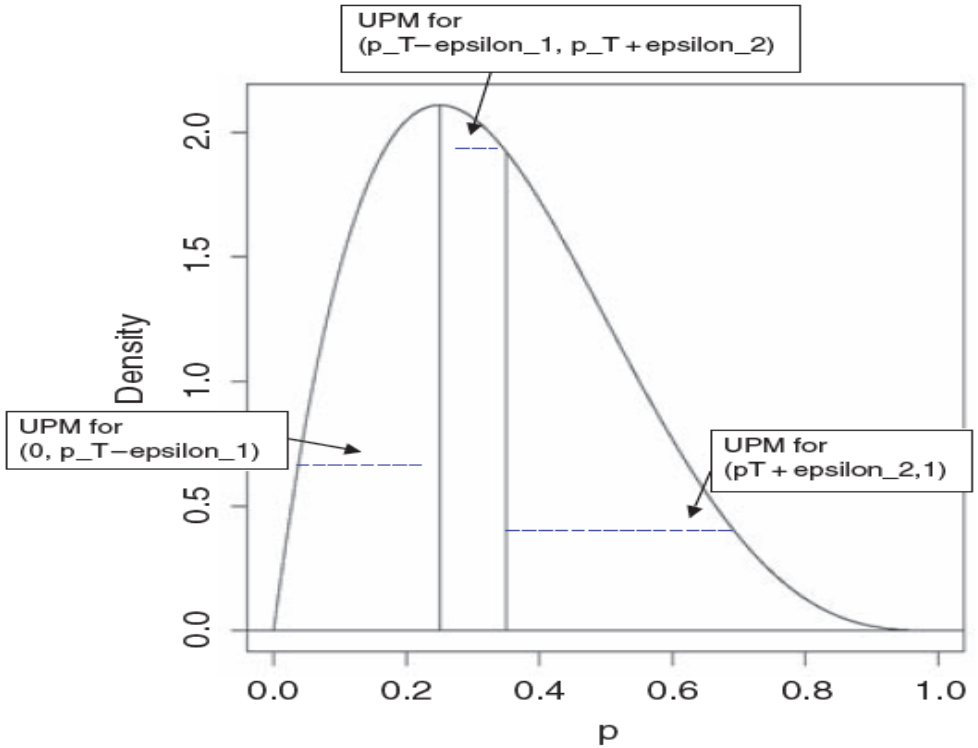
  > If $\text{pr}(p_j > \phi | m_j, n_j) > 0.95$ and $n_j \geq 3$, dose levels $j$ and higher are eliminated from the trial, and the trial is terminated if the first dose level is eliminated,

  where $\text{pr}(p_j > \phi | m_j, n_j)$ can be evaluated based on a beta-binomial model.
- The dose elimination boundaries can be tabulated before the initiation of the trial.

# Simulation study

- We considered six dose levels with the target toxicity probability $\phi = 0.25$,
- The maximum sample size was 12 cohorts, with a cohort size of 3
- Set $\phi_1 = 0.15$ and $\phi_2 = 0.35$
- Compared the proposed designs with the “3+3” design, the CRM, the modified toxicity probability interval (mTPI) design (Ji, et al., 2010).
- We simulated 10,000 trials.

# mTPI design


UPM for
(p_T−epsilon_1, p_T + epsilon_2)
UPM for
(0, p_T−epsilon_1)
UPM for
(pT + epsilon_2,1)
Density
0.0
0.5
1.0
1.5
2.0
0.0
0.2
0.4
0.6
0.8
1.0
p

# Simulation study

- For each simulated trial, the toxicity scenario (i.e, the true toxicity probabilities of the six doses) was randomly generated.
  1. randomly select, with equal probabilities, one of the six dose levels, say $j$, as the MTD
  2. generate the toxicity probability of the MTD $p_j$
  3. generate $p_{j-1}$ and $p_{j+1}$ (i.e., the toxicity probabilities of two doses adjacent to the MTD) under the constraint that $p_j$ is closest to $\phi$.
  4. successively generate the toxicity probabilities for the remaining levels

# Simulation study

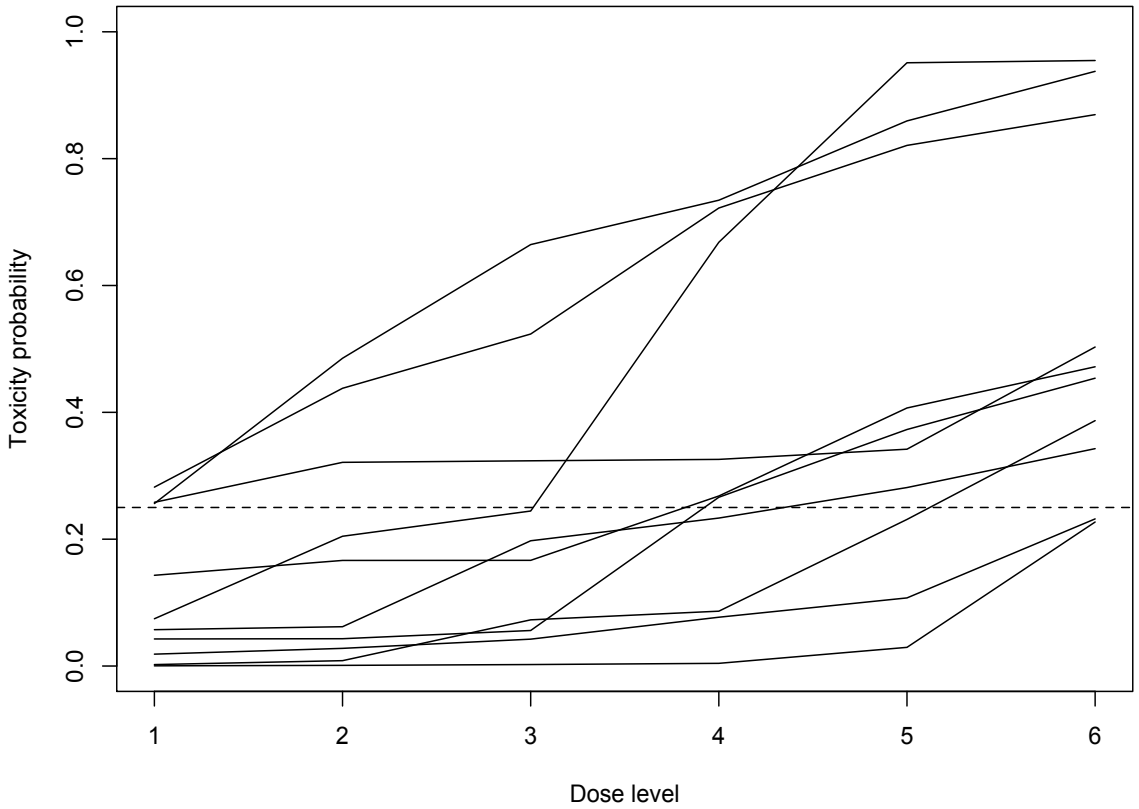



Figure : Ten randomly generated dose-toxicity curves

# Simulation results

Table : Simulation results when the average probability difference around the target = 0.1

| Design | Selection % of MTD | % of patients at MTD | % of $n_{MTD} < n/J$ | Average toxicty rate | % of toxicty rate $> \phi_2$ |
|---|---|---|---|---|---|
| 3+3 | 27.9 | 27.1 | 33.0 | 22.0 | 7.8 |
| mTPI | 45.0 | **35.4** | 40.9 | 21.3 | 5.2 |
| CRM | 43.3 | 34.0 | 44.3 | 20.8 | 5.4 |
| Optimal | **45.0** | 32.4 | **29.9** | **20.6** | **4.7** |

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Table : Simulation results when the average probability difference around the target = 0.07

| Design | Selection % of MTD | % of patients at MTD | % of $n_{MTD} < n/J$ | Average toxicty rate | % of toxicty rate $> \phi_2$ |
|---|---|---|---|---|---|
| 3+3 | 23.3 | 24.5 | 41.0 | 23.8 | 10.4 |
| mTPI | 36.7 | **29.4** | 50.0 | 21.4 | 5.5 |
| CRM | 34.5 | 28.8 | 54.3 | 21.0 | 5.8 |
| Optimal | **37.3** | 28.6 | **38.1** | **20.9** | **5.4** |

# Simulation results

Table : Simulation results when the average probability difference around the target = 0.15

| Design | Selection % of MTD | % of patients at MTD | % of $n_{MTD} < n/J$ | Average toxicty rate | % of toxicty rate $> \phi_2$ |
|---|---|---|---|---|---|
| 3+3 | 35.6 | 31.0 | 21.4 | 20.3 | 6.7 |
| mTPI | 56.9 | 44.0 | 27.1 | 21.1 | 4.7 |
| CRM | **59.6** | **44.3** | 27.4 | 20.7 | 4.6 |
| Optimal | 58.3 | 39.4 | **17.9** | **20.0** | **4.2** |

# Simulation results

- The “3+3" design had the worst performance
- Compared to the CRM and mTPI, the optimal design yielded comparable results for the “average" measures.
- In terms of the measures of “bad" runs, the optimal design performed substantially better than the CRM and mTPI.

# Simulation results

- The “3+3" design had the worst performance
- Compared to the CRM and mTPI, the optimal design yielded comparable results for the “average" measures.
- In terms of the measures of “bad" runs, the optimal design performed substantially better than the CRM and mTPI.
- From an implementation point of view, such an improvement is of great practical importance because we rarely run a trial more than a few times.
- What really concerns us is the likelihood of the current trial being a “bad" trial, not the trial designs average performance over thousands of runs, such as in a simulation study.

# Software

- We have prepared easy-to-use software (with detailed tutorial) to implement the proposed design.
- Three R functions
  - `get.boundary(···)`; This function is used to generate escalation and deescalation boundaries for the optimal interval design;

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  - `dose.select(···)`; This function is used to select the MTD at the end of the trial based on isotonically transformed estimates;
  - `get.oc(···)`; This function is used to generate operating characteristics for the proposed trial designs.

# Software

- The software is available for downloading at http://odin.mdacc.tmc.edu/~yyuan/index_code.html,
  or MD Anderson Biostatistics software download website https://biostatistics.mdanderson.org/SoftwareDownload/

# Illustration

Using the software to design a phase I trial

- Assume six dose level, target $\phi = 0.3$
- The maximum sample size of 10 cohorts of size 3

# The optimal interval design

1. The first cohort are treated at the lowest dose level.
2. At the current dose level $j$, conduct dose escalation/deescalation as follows:

| | Number of patients treated at the current dose ($n_j$) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Boundary | 3 | 6 | 9 | 12 | 15 | 18 | 21 | 24 | 27 | 30 |
| Escalate if # of DLT <= | 0 | 1 | 2 | 2 | 3 | 4 | 5 | 5 | 6 | 7 |
| Deescalate if # of DLT >= | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
| Eliminate if # of DLT >= | 3 | 4 | 5 | 7 | 8 | 9 | 10 | 11 | 12 | 14 |

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| Deescalate if # of DLT >= | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
| Eliminate if # of DLT >= | 3 | 4 | 5 | 7 | 8 | 9 | 10 | 11 | 12 | 14 |

- This table is all the clinician needs to run the trial!
- The trial conduct does not need any software support

# The optimal interval design

1. The proposed design allows the cohort size to vary from one cohort to another.
2. Enumerate all possible boundaries

| | Number of patients treated at the current dose ($n_j$) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Boundary | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| Escalate if # of DLT <= | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 2 | 2 |
| Deescalate if # of DLT >= | 1 | 1 | 2 | 2 | 2 | 3 | 3 | 3 | 4 | 4 |
| Eliminate if # of DLT >= | NA | NA | 3 | 3 | 4 | 4 | 5 | 5 | 5 | 6 |

| | Number of patients treated at the current dose ($n_j$) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Boundary | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 |
| Escalate if # of DLT <= | 2 | 2 | 3 | 3 | 3 | 3 | 4 | 4 | 4 | 4 |
| Deescalate if # of DLT >= | 4 | 5 | 5 | 6 | 6 | 6 | 7 | 7 | 7 | 8 |
| Eliminate if # of DLT >= | 6 | 7 | 7 | 8 | 8 | 8 | 9 | 9 | 9 | 10 |

- So the decision can be made at any time of the trial!

# Discussion

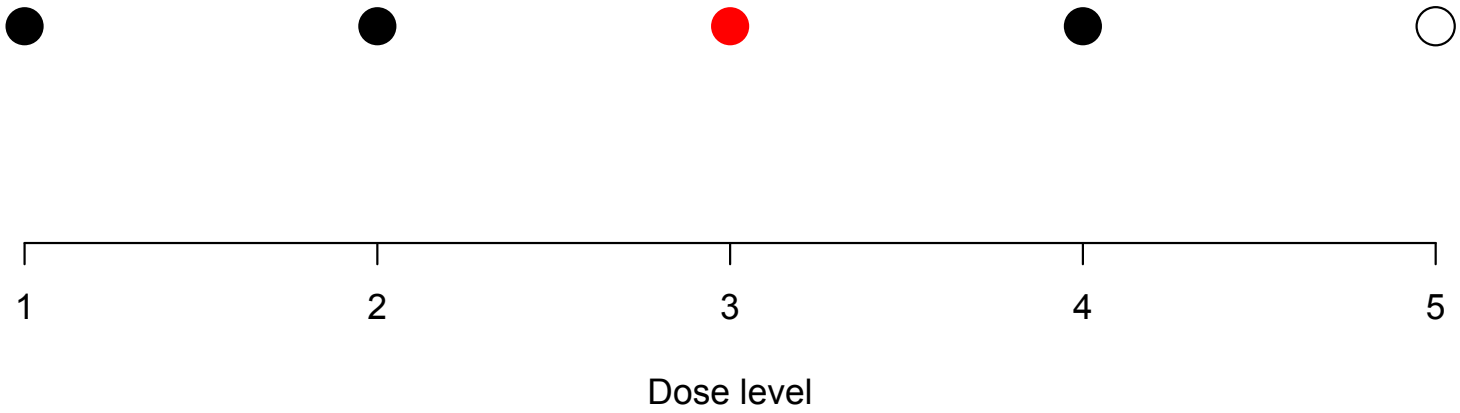
Does the proposed design lose substantial information?

# Discussion

Does the proposed design lose substantial information?

- All data are used for select the MTD
- Only data at the current dose are used to determine dose assignment, but the sequential dose-escalation procedure implicitly accounts for the majority of information from other doses!

# Discussion



# Discussion

- The proposed decision-making framework is very flexible
- Partition the decision error

$$\begin{aligned}\alpha &\equiv \text{pr}(\text{incorrect decision}) \\ &= \underbrace{\text{pr}(H_0)\text{pr}(\bar{\mathcal{R}}|H_0)}_{a} + \underbrace{\text{pr}(H_1)\text{pr}(\bar{\mathcal{E}}|H_1)}_{b} + \underbrace{\text{pr}(H_2)\text{pr}(\bar{\mathcal{D}}|H_2)}_{c}\end{aligned}$$

- A minimax design that minimizes the maximum of these three types of errors.

# Discussion

- We can also classify the decision error into errors of making incorrect decisions of escalation, deescalation and dose level retainment

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

- Assign the appropriate weight to each type of error to reflect its relative importance, and minimize the weighted decision error rate
  - Penalize more for incorrect dose escalations

# Global optimal interval design

- Use three composite hypotheses to define decision errors

$$\begin{aligned} H_0: &\quad \phi_1 < p_j < \phi_2 \\ H_1: &\quad 0 \le p_j \le \phi_1 \\ H_2: &\quad \phi_2 \le p_j \le 1, \end{aligned}$$

- Then, the average decision error rate is given by

$$\begin{aligned} & \text{pr}(\text{incorrect decision}) \\ = \; & \text{pr}(H_0) \int \pi(p_j|H_0)\text{pr}(\bar{\mathcal{R}}|p_j, H_0)\, \text{d}p_j + \text{pr}(H_1) \int \pi(p_j|H_1)\text{pr}(\bar{\mathcal{E}}|p_j, H_1)\, \text{d}p_j \\ & + \text{pr}(H_2) \int \pi(p_j|H_2)\text{pr}(\bar{\mathcal{D}}|p_j, H_2)\, \text{d}p_j \end{aligned}$$

- In our paper, we call the resulting design as the global optimal interval design and the design based on three point hypotheses as the local optimal interval design.

# Reference

Liu, S. and Yuan, Y. (2012) Optimal Interval Designs for Phase I Clinical Trials *Statistics in Medicine*, revision invited.

Thank you !