Bayesian optimal interval design in phase I oncology trials

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Introduction

Methods

Using Stata
Oncology Trials

- Phase I
  - Find maximum tolerated dose
- Phase II
  - Is drug efficacious-active
- Phase III
  - Comparative study, assess effectiveness and its role in clinical practice
- Phase IV
  - Typically longer term studies, may have narrower focus, further study toxicity
Phase I oncology trials

- Goal to find maximum tolerated dose (MTD) with some target toxicity rate $\phi$
- 3+3
  - Most common
  - Poor performance/easy to implement
- Continual reassessment method (CRM)
  - Good performance/difficult to implement
Good Phase I Trial

- Intuitive—both by clinicians and statisticians
- Implementation should be easy
- Sound statistical properties
- Good/Superior operating characteristics
Conduct

- Treat first cohort at lowest or prespecified dose
- Decide to
Conduct

- Treat first cohort at lowest or prespecified dose
- Decide to
  - 1. Escalate
Conduct

- Treat first cohort at lowest or prespecified dose
- Decide to:
  1. Escalate
  2. Retain
Conduct

- Treat first cohort at lowest or prespecified dose
- Decide to
  1. Escalate
  2. Retain
  3. De-escalate
Conduct

- Treat first cohort at lowest or prespecified dose
- Decide to
  - 1. Escalate
  - 2. Retain
  - 3. De-escalate
- Repeat till decision on MTD is made
## Conduct

- Treat first cohort at lowest or prespecified dose
- Decide to
  - 1. Escalate
  - 2. Retain
  - 3. De-escalate
- Repeat till decision on MTD is made

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>1</th>
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Ideally

- If know true toxicity probability of current dose level $j$, $p_j$
- Decide
Ideally

- If know true toxicity probability of current dose level $j$, $p_j$
- Decide
  - 1. **Escalate** if $p_j < \phi$
Ideally

- If know true toxicity probability of current dose level $j$, $p_j$
- Decide
  1. **Escalate** if $p_j < \phi$
  2. **Retain** if $p_j = \phi$
Ideally

- If know true toxicity probability of current dose level \( j \), \( p_j \)
- Decide
  1. Escalate if \( p_j < \phi \)
  2. Retain if \( p_j = \phi \)
  3. De-escalate if \( p_j > \phi \)
Ideally

- If know true toxicity probability of current dose level $j$, $p_j$
- Decide
  1. Escalate if $p_j < \phi$
  2. Retain if $p_j = \phi$
  3. De-escalate if $p_j > \phi$

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</tr>
</thead>
<tbody>
<tr>
<td>Toxicity</td>
<td>0.10</td>
<td>0.20</td>
<td>0.30</td>
<td>0.40</td>
<td>0.50</td>
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Ideally

- If know true toxicity probability of current dose level $j$, $p_j$
- Decide
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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.
Dose assignment complicated because $p_j$ is unknown

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<tr>
<td>Toxicity</td>
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We estimate $p_j$ based on data and make decision

- Observed toxicity rate $= \frac{t_j}{n_j} \implies$ make decision
- This often incorrect because of small sample size and estimation uncertainty
Dose assignment complicated because $p_j$ is unknown

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Retain when current dose is above/below MTD
Dose assignment complicated because $p_j$ is unknown

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- Observed toxicity rate $= \frac{t_j}{n_j}$ $\implies$ make decision
- This often incorrect because of small sample size and estimation uncertainty

1. **Retain** when current dose is above/below MTD
2. **Escalate** when current dose is above MTD
Dose assignment complicated because $p_j$ is unknown

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- Observed toxicity rate $= \frac{t_j}{n_j} \implies$ make decision
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  1. **Retain** when current dose is above/below MTD
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Dose assignment complicated because $p_j$ is unknown

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We estimate $p_j$ based on data and make decision

- Observed toxicity rate $= \frac{t_j}{n_j}$ $\Rightarrow$ make decision
- This often incorrect because of small sample size and estimation uncertainty

1. **Retain** when current dose is **above/below** MTD
2. **Escalate** when current dose is **above** MTD
3. **De-escalate** when current dose is **below** MTD
Motivation

- Minimize these decision errors
- Get as close as possible to ideal case
- Insures patient safety and adheres to ethical standards
The optimal interval design

1. Treat first cohort at lowest or prespecified dose
2. At current dose level j:
   (a) if $\hat{p}_j \leq \lambda_{1j}$, escalate
   (b) if $\hat{p}_j \geq \lambda_{2j}$, de-escalate
   (c) otherwise, $(\lambda_{1j} < \hat{p}_j < \lambda_{2j})$, retain
   where $\hat{p}_j$ is observed toxicity rate $= \frac{t_j}{n_j}$ and $\lambda_{1j}$ and $\lambda_{2j}$ are prespecified dose escalation and de-escalation boundaries
3. Continue (2) until maximum sample size is reached
The optimal interval design

How to select the interval boundaries $\lambda_{1j}$ and $\lambda_{2j}$ to minimize the decision error of dose assignment?
How to select the interval boundaries $\lambda_{1j}$ and $\lambda_{2j}$ to minimize the decision error of dose assignment?
To minimize incorrect decision making, the definition of correct and incorrect decisions will be defined as follows.

\[ H_{0j} : \quad p_j = \phi \]
\[ H_{1j} : \quad p_j = \phi_1 \]
\[ H_{2j} : \quad p_j = \phi_2 \]
Setup

To minimize incorrect decision making, the definition of correct and incorrect decisions will be defined as follows.

- \( H_{0j} : p_j = \phi \)
- \( H_{1j} : p_j = \phi_1 \)
- \( H_{2j} : p_j = \phi_2 \)

- \( \phi_1 \) denotes the highest toxicity probability deemed subtherapeutic so that dose escalation should be made
- \( \phi_2 \) denotes the lowest toxicity probability deemed overly toxic so that dose de-escalation is required
Assume $Pr(H_0) = Pr(H_1) = Pr(H_2) = 1/3$, a priori, the current dose is equally likely to be below, above, or equal to the MTD.

Decision error rate is minimized when

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

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

The dose escalation/de-escalation boundaries are independent of $n_j$ and $j$ when the non-informative prior is used.

Same set of boundaries can be used throughout the trial.
At end of trial, based on observed data, we select the MTD dose whose isotonic estimate of toxicity rate is closest to $\phi$

Under proposed optimal dose assignment, we tend to treat patients at or close to the MTD, thus leads to high probability of selecting the correct MTD because most data and statistical power are concentrated around the MTD
For patient safety, we impose the following dose elimination rule:

- If $Pr(p_j > \phi | t_j, n_j) > \pi_*$ and $n_j \geq 3$, dose levels $j$ and higher are eliminated from the trial, where $Pr(p_j > \phi | t_j, n_j)$ can be evaluated based on a beta-binomial model.
optinterval, getboundary selectmtd oc design(#) target(#) ncohort(#) cohort(#) saf(#) tox(#) cut(#)
npts(numlist) ntox(numlist) startdose(#) truep(numlist) ntrials(#)
Options

```
optinterval, getboundary selectmtd oc design(#) target(#) ncohort(#) cohort(#) saf(#) tox(#) cut(#)
npts(numlist) ntox(numlist) startdose(#) truep(numlist) ntrials(#)```

- `getboundary` specifies to calculate dose escalation rules for a proposed design
Options

\texttt{optinterval, getboundary selectmtd oc design(#) target(#) ncohort(#) cohort(#) saf(#) tox(#) cut(#)}
\texttt{npts(\texttt{numlist}) ntolx(\texttt{numlist}) startdose(#)}
\texttt{truep(\texttt{numlist}) ntrials(#)}

- \texttt{getboundary} specifies to calculate dose escalation rules for a proposed design
- \texttt{selectmtd} specifies to find the MTD at the end of a trial
Options

\texttt{optinterval, getboundary selectmtd \textbf{oc} design(#) target(#)}
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- \texttt{getboundary} specifies to calculate dose escalation rules for a proposed design
- \texttt{selectmtd} specifies to find the MTD at the end of a trial
- \texttt{oc} specifies to calculate operating characteristics for a proposed design
Options

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- \texttt{design(#)}: 1 specifies to use the local optimal design; 2 specifies the global optimal design; the default is 1.
Options

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optinterval, getboundary selectmtd oc design(#) target(#)
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- **design(#) 1** specifies to use the local optimal design; 2 specifies the global optimal design; the default is 1
- **target(#)** specifies the target toxicity rate; this option is required and must be > 0.05 and ≤ 0.60
Options

\[ \text{optinterval, getboundary selectmtd oc design(#) target(#)} \]
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Introduction Methods Using Stata Conclusion

Options

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```plaintext
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- cohort(#) specifies the cohort size; the default is 1
optinterval, getboundary selectmtd oc design(#) target(#) ncohort(#) cohort(#) saf(#) tox(#) cut(#) npts(numlist) ntox(numlist) startdose(#) truep(numlist) ntrials(#)  

**saf(#)** specifies the highest toxicity probability that is deemed subtherapeutic (i.e., below the MTD) such that the dose escalation should be made. The default value is 0.6*target
Options

```
optinterval, getboundary selectmtd oc design(#) target(#)  
ncohort(#) cohort(#) saf(#) tox(#) cut(#)  
npts(numlist) ntox(numlist) startdose(#)  
truep(numlist) ntrials(#)
```

- `saf(#)` specifies the highest toxicity probability that is deemed subtherapeutic (i.e., below the MTD) such that the dose escalation should be made. The default value is 0.6*target—\(\phi_1\).
optinterval, getboundary selectmtd oc design(#) target(#) ncohort(#) cohort(#) saf(#) tox(#) cut(#) npts(numlist) ntox(numlist) startdose(#) truep(numlist) ntrials(#)

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- tox(#) the lowest toxicity probability that is deemed overly toxic such that the dose de-escalation is required. The default value is 1.4*target.
Introduction

Methods

Using Stata

Conclusion

Options

optinterval, getboundary selectmtd oc design(#) target(#)
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Options

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- tox(#) the lowest toxicity probability that is deemed overly toxic such that the dose de-escalation is required. The default value is 1.4*target.

- cut(#) specifies the cutoff to eliminate the overly toxic dose for safety monitoring; the default is 0.95.
Options

- `optinterval`, `getboundary`, `selectmtd`, `oc design(#) target(#)`  
  `ncohort(#) cohort(#) saf(#) tox(#) cut(#)`  
  `npts(numlist) ntox(numlist) startdose(#)`  
  `truep(numlist) ntrials(#)`

- `saf(#)` specifies the highest toxicity probability that is deemed subtherapeutic (i.e., below the MTD) such that the dose escalation should be made. The default value is 0.6*target

- `tox(#)` the lowest toxicity probability that is deemed overly toxic such that the dose de-escalation is required. The default value is 1.4*target

- `cut(#)` specifies the cutoff to eliminate the overly toxic dose for safety monitoring; the default is 0.95—π∗
Options

optinterval, getboundary selectmtd oc design(#) target(#) ncohort(#) cohort(#) saf(#) tox(#) cut(#)
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npts(numlist) specifies the number of patients treated at each dose at the end of the trial; this option is required when option selectmtd is specified
Options

\texttt{optinterval, getboundary selectmtd oc design(#) target(#)}
\texttt{ncohort(#) cohort(#) saf(#) tox(#) cut(#)}
\texttt{npts(\textit{numlist}) ntox(\textit{numlist}) startdose(#)}
\texttt{truep(\textit{numlist}) ntrials(#)}

- \texttt{\textit{npts}(\textit{numlist})} specifies the number of patients treated at each dose at the end of the trial; this option is required when option selectmtd is specified.
- \texttt{\textit{ntox}(\textit{numlist})} specifies the number of toxicities at each dose at the end of the trial; this option is required when option \texttt{selectmtd} is specified.
optinterval, getboundary selectmtd oc design(#) target(#) ncohort(#) cohort(#) saf(#) tox(#) cut(#) npts(numlist) ntox(numlist) startdose(#) truep(numlist) ntrials(#)

- **startdose(#)** specifies the starting dose for the trial; the default is 1
Options

optinterval, getboundary selectmtd oc design(#) target(#) ncohort(#) cohort(#) saf(#) tox(#) cut(#) npts(numlist) ntox(numlist) startdose(#) truep(numlist) ntrials(#)

- **startdose(#)** specifies the starting dose for the trial; the default is 1

- **truep(numlist)** specifies the true toxicity probabilities for each dose; this option is required when option **oc** is specified
Options

```
optinterval, getboundary selectmtd oc design(#) target(#)  
ncohort(#) cohort(#) saf(#) tox(#) cut(#)  
npts(numlist) ntox(numlist) startdose(#)  
truep(numlist) ntrials(#)  
```

- `startdose(#)`: specifies the starting dose for the trial; the default is 1
- `truep(numlist)`: specifies the true toxicity probabilities for each dose; this option is required when option `oc` is specified
- `ntrials(#)`: specifies the number of trials to simulate when calculating operating characteristics, the default is 10,000
Design trial

- Target toxicity rate $\phi$ of 0.30
- Enroll 10 cohorts in sample sizes of 3 patients
- Maximum sample size of 30 patients
- 6 doses
Bayesian optimal interval design in phase I oncology trials

Operating Characteristics - Scenario 1

```
. optinterval, oc target(0.30) ncohort(10) cohort(3) truep(0.30 0.35 0.40 0.45 0.50 0.60) ntrials(1000)
```

<table>
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<tr>
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</tr>
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<tbody>
<tr>
<td>Pr(Toxicity)</td>
<td>0.30</td>
<td>0.35</td>
<td>0.40</td>
<td>0.45</td>
<td>0.50</td>
<td>0.60</td>
</tr>
<tr>
<td>% Selected</td>
<td>47.90</td>
<td>22.00</td>
<td>11.30</td>
<td>2.20</td>
<td>1.30</td>
<td>0.10</td>
</tr>
<tr>
<td>Avg Toxicity</td>
<td>4.76</td>
<td>2.54</td>
<td>1.12</td>
<td>0.34</td>
<td>0.07</td>
<td>0.01</td>
</tr>
<tr>
<td>Avg Patients</td>
<td>16.16</td>
<td>7.09</td>
<td>2.81</td>
<td>0.74</td>
<td>0.15</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Avg Patients = 26.98
Avg Toxicities = 8.84

% Dose 1 overly toxic = 15.2
### Operating Characteristics - Scenario 2

```
. optinterval, oc target(0.30) ncohort(10) cohort(3) truep(0.10 0.20 0.30 0.40 0.50 0.60) ntrials(1000)
```

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<tr>
<td>Pr(Toxicity)</td>
<td>0.10</td>
<td>0.20</td>
<td>0.30</td>
<td>0.40</td>
<td>0.50</td>
<td>0.60</td>
</tr>
<tr>
<td>% Selected</td>
<td>3.40</td>
<td>29.30</td>
<td>39.90</td>
<td>21.90</td>
<td>4.50</td>
<td>0.70</td>
</tr>
<tr>
<td>Avg Toxicity</td>
<td>0.54</td>
<td>1.91</td>
<td>2.70</td>
<td>1.65</td>
<td>0.58</td>
<td>0.08</td>
</tr>
<tr>
<td>Avg Patients</td>
<td>5.58</td>
<td>9.77</td>
<td>8.97</td>
<td>4.34</td>
<td>1.14</td>
<td>0.13</td>
</tr>
</tbody>
</table>

Avg Patients = 29.93
Avg Toxicities = 7.46

% Dose 1 overly toxic = .3
### Operating Characteristics - Scenario 3

```
* optinterval, oc target(0.30) ncohorts(10) cohort(3) truem(0.05 0.10 0.15 0.20 0.25 0.30) ntrials(1000)

<table>
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<tbody>
<tr>
<td>Pr(Toxicity)</td>
<td>0.05</td>
<td>0.10</td>
<td>0.15</td>
<td>0.20</td>
<td>0.25</td>
<td>0.30</td>
</tr>
<tr>
<td>% Selected</td>
<td>0.20</td>
<td>2.80</td>
<td>10.90</td>
<td>21.60</td>
<td>30.40</td>
<td>34.00</td>
</tr>
<tr>
<td>Avg Toxicity</td>
<td>0.22</td>
<td>0.56</td>
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Avg Patients = 29.98
Avg Toxicities = 5.26

% Dose 1 overly toxic = .1
### Table for design write-up

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Bayesian optimal interval design in phase I oncology trials

Decision Boundaries

```
. optinterval, getboundary target(0.3) ncohort(10) cohort(3)

Escalate dose if the observed toxicity rate at the current dose <= .23649069
Deescalate dose if the observed toxicity rate at the current dose >= .35851946
```

This is equivalent to the following decision boundaries

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<th>Deescalate (if # DLT &gt;=)</th>
<th>Eliminate (if # DLT &gt;=)</th>
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## Decision Boundaries—design write-up

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This is all a clinician needs to conduct the trial!!!!

Cohort 1 (1/3) → Retain Dose 1
Cohort 2 (1/6) → Escalate to Dose 2
Cohort 3 (2/3) → De-escalate to Dose 1
Cohort 4 (2/9) → Escalate to Dose 2
Cohort 5 (2/6) → Retain Dose 2
Cohort 6 ...

Bryan Fellman, MS  Ying Yuan, PhD

Bayesian optimal interval design in phase I oncology trials
### Decision Boundaries–design write-up

<table>
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<tr>
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This is all a clinician needs to conduct the trial!!!!
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<td>Eliminate if # DLT ≥</td>
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</tr>
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</table>

This is all a clinician needs to conduct the trial!!!!

1. Cohort 1 (1/3) → Retain Dose 1
### Decision Boundaries—design write-up

<table>
<thead>
<tr>
<th>Decision</th>
<th># of Patients Treated at Current Dose Level</th>
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<tbody>
<tr>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Escalate if # DLT ≤</td>
<td>0</td>
</tr>
<tr>
<td>De-escalate if # DLT ≥</td>
<td>2</td>
</tr>
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This is all a clinician needs to conduct the trial!!!!!

1. Cohort 1 (1/3) → Retain Dose 1
2. Cohort 2 (1/6) → Escalate to Dose 2
## Decision Boundaries—design write-up

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This is all a clinician needs to conduct the trial!!!!

1. Cohort 1 (1/3) → Retain Dose 1
2. Cohort 2 (1/6) → Escalate to Dose 2
3. Cohort 3 (2/3) → De-escalate to Dose 1
Decision Boundaries—design write-up

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</thead>
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<tr>
<td>Escalate if # DLT ≤</td>
<td>0  1  2  2  3  4  4  5  6  7</td>
</tr>
<tr>
<td>De-escalate if # DLT ≥</td>
<td>2  3  4  5  6  7  8  9  10 11</td>
</tr>
<tr>
<td>Eliminate if # DLT ≥</td>
<td>3  4  5  7  8  9 10 11 12 14</td>
</tr>
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</table>

This is all a clinician needs to conduct the trial!!!!

1. Cohort 1 (1/3) → Retain Dose 1
2. Cohort 2 (1/6) → Escalate to Dose 2
3. Cohort 3 (2/3) → De-escalate to Dose 1
4. Cohort 4 (2/9) → Escalate to Dose 2
### Decision Boundaries—design write-up

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This is all a clinician needs to conduct the trial!!!!

1. Cohort 1 (1/3) → Retain Dose 1
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3. Cohort 3 (2/3) → De-escalate to Dose 1
4. Cohort 4 (2/9) → Escalate to Dose 2
5. Cohort 5 (2/6) → Retain Dose 2

Bryan Fellman, MS  Ying Yuan, PhD  Bayesian optimal interval design in phase I oncology trials
### Decision Boundaries—design write-up

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<td>3   6   9   12  15  18  21  24  27  30</td>
</tr>
<tr>
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<td>0 1  2  2   2  3   4   4   5   6   7</td>
</tr>
<tr>
<td>De-escalate if # DLT ≥</td>
<td>2 3  4  5   6  7   8   9   10  11  12</td>
</tr>
<tr>
<td>Eliminate if # DLT ≥</td>
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This is all a clinician needs to conduct the trial!!!!

1. Cohort 1 (1/3) → Retain Dose 1
2. Cohort 2 (1/6) → Escalate to Dose 2
3. Cohort 3 (2/3) → De-escalate to Dose 1
4. Cohort 4 (2/9) → Escalate to Dose 2
5. Cohort 5 (2/6) → Retain Dose 2
6. ...
Selecting MTD

```
. optinterval, selectmtd target(0.30) npts(3 6 15 6 0 0) ntox(0 1 3 3 0 0)

The MTD is dose level 3
```
Conclusions

- One table is all clinician needs to run trial
- Trial conduct software is not needed
- Intuitive—both by clinicians and statisticians
- Implementation is easy
- Sound statistical properties
- Good/Superior operating characteristics
THANK YOU!
Hypothesis comments

- $H_1$ and $H_2$, or $\delta_1 = \phi_1 - \phi$ and $\delta_2 = \phi_2 - \phi$, represent the minimal differences 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.

- The approach is analogous to sample size determination and power calculation.
The correct decisions under $H_0$, $H_1$, and $H_2$ are $R$, $E$, and $D$, respectively, where $R$, $E$, and $D$ denote dose retainment, escalation, and de-escalation of the current dose level.

The incorrect decisions under $H_0$, $H_1$, and $H_2$ are $\tilde{R}$, $\tilde{E}$, and $\tilde{D}$, respectively, where $\tilde{R}$, $\tilde{E}$, and $\tilde{D}$ denote the decisions complementary to $R$, $E$, and $D$.
Decision error rate

- Assign each of the hypothesis a prior probability
  \( Pr(H_k), k = 0, ..., 2 \)
- The probability of making an incorrect decision (or decision error rate) at each of the dose assignments is:
Assign each of the hypothesis a prior probability \( Pr(H_k), k = 0, \ldots, 2 \)

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

\[
\alpha \equiv Pr(\text{incorrect decision})
\]
Decision error rate

- Assign each of the hypothesis a prior probability $Pr(H_k), k = 0, ..., 2$
- The probability of making an incorrect decision (or decision error rate) at each of the dose assignments is:

$$\alpha \equiv Pr(\text{incorrect decision})$$

$$= Pr(H_0)Pr(\bar{R}|H_0)$$
Decision error rate

- Assign each of the hypothesis a prior probability $Pr(H_k)$, $k = 0, \ldots, 2$
- The probability of making an incorrect decision (or decision error rate) at each of the dose assignments is:

$$\alpha \equiv Pr(\text{incorrect decision}) = Pr(H_0)Pr(\tilde{R} \mid H_0) + Pr(H_1)Pr(\tilde{E} \mid H_1)$$
Assign each of the hypothesis a prior probability \( Pr(H_k), k = 0, ..., 2 \)

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

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Decision error rate

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\alpha \equiv \Pr(\text{incorrect decision}) = \Pr(H_0)\Pr(\tilde{R}|H_0) + \Pr(H_1)\Pr(\tilde{E}|H_1) + \Pr(H_2)\Pr(\tilde{D}|H_2) \\
= \Pr(H_0)\Pr(\hat{p}_j < \lambda_1 \cup \hat{p}_j > \lambda_2|H_0) + \Pr(H_1)\Pr(\hat{p}_j > \lambda_1|H_1) \\
+ \Pr(H_2)\Pr(\hat{p}_j < \lambda_2|H_2)
\]
Assign each of the hypothesis a prior probability \(Pr(H_k), k = 0, \ldots, 2\)

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

\[
\alpha \equiv Pr(\text{incorrect decision})
= Pr(H_0)Pr(\hat{R} | H_0) + Pr(H_1)Pr(\hat{E} | H_1) + Pr(H_2)Pr(\hat{D} | H_2)
= Pr(H_0)Pr(\hat{p}_j < \lambda_{1j} \cup \hat{p}_j > \lambda_{2j} | H_0) + Pr(H_1)Pr(\hat{p}_j > \lambda_{1j} | H_1)
+ Pr(H_2)Pr(\hat{p}_j < \lambda_{2j} | H_2)
= Pr(H_0)\{Bin(n_j \lambda_{1j}; n_j, \phi) + 1 - Bin(n_j \lambda_{2j} - 1; n_j, \phi)\}
+ Pr(H_1)\{1 - Bin(n_j \lambda_{1j}; n_j, \phi_1)\}
+ Pr(H_2)Bin(n_j \lambda_{2j} - 1; n_j, \phi_2)
Theorem 1—$\lambda_{1j}$ and $\lambda_{2j}$

- $\lambda_{1j}$ is the boundary at which the posterior probability of $H_1$ becomes more likely than that of $H_0$, i.e.,
  $$\lambda_{1j} = \arg\max_{\hat{p}_j} (\Pr(H_1|n_j, t_j) > \Pr(H_0|n_j, t_j))$$

- $\lambda_{2j}$ is the boundary at which the posterior probability of $H_2$ becomes more likely than that of $H_0$, i.e.,
  $$\lambda_{2j} = \arg\max_{\hat{p}_j} (\Pr(H_2|n_j, t_j) > \Pr(H_0|n_j, t_j))$$
Theorem 1—$\lambda_{1j}$ and $\lambda_{2j}$

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

This provides intuitive justification for escalation/de-escalation rules!!
The proposed optimal interval design is (long-memory) coherent in the sense that the probability of dose escalation (or de-escalation) is zero when the observed toxicity rate \( \hat{p}_j \) at the current dose is higher (or lower) than the target toxicity rate \( \phi \).
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.
Simulation study

- Considered 6 dose levels with target toxicity rate $\phi = 0.25$
- $N = 36$ with cohort size of 3
- Set $\phi_1 = 0.15$ and $\phi_2 = 0.35$
- Simulated 10,000 trials
- Compared the proposed designs with the 3+3 and the CRM
Simulation results

- 3+3 design had the worst performance
- Compared to the CRM, the optimal design yielded comparable results for the "average" measures
- In terms of the risk of being a bad trial, the optimal design performed substantially better than the CRM
  - Bad trial was defined in terms of risk of poor allocation and risk of high toxicity