Bayesian optimal interval design in phase I oncology trials

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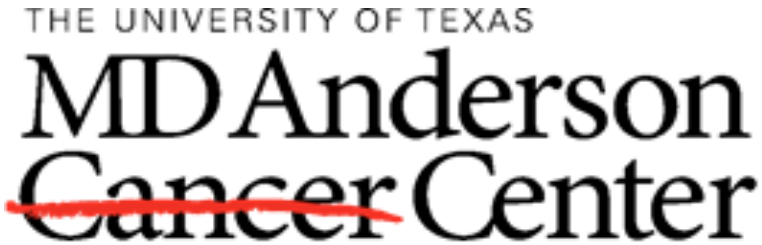


Outline

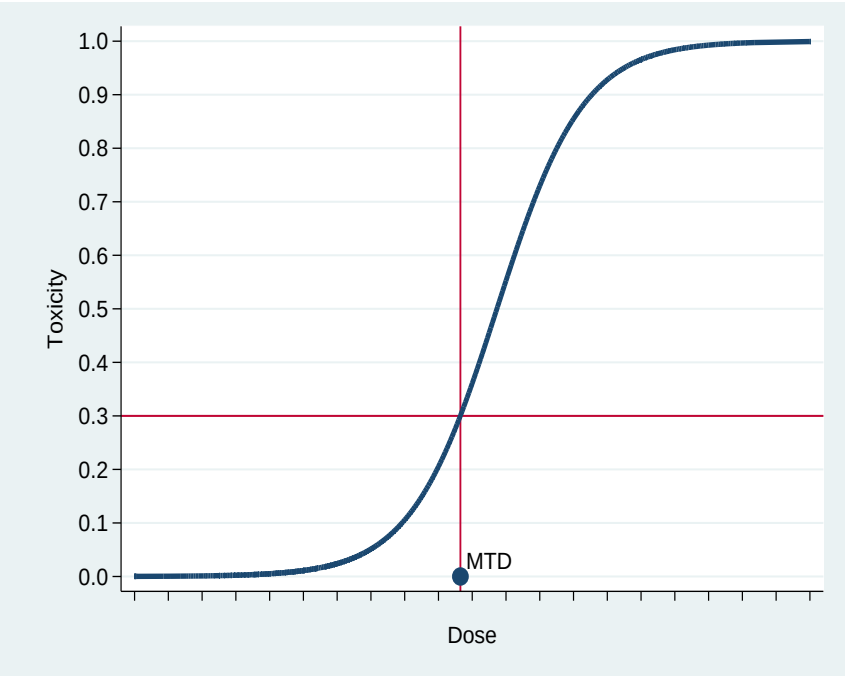
- Introduction
- Methods
- Using Stata

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 ϕ
- 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
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- Repeat till decision on MTD is made

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Dose Level					
1	2	3	4	5	6

Ideally

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

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- Decide
  1. Escalate if $p_j < \phi$
  2. Retain if $p_j = \phi$

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

	Dose Level					
	1	2	3	4	5	6
Toxicity	0.10	0.20	0.30	0.40	0.50	0.60

Ideally

- If know true toxicity probability of current dose level j, p_j
- Decide
  1. Escalate if $p_j < \phi$
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	Dose Level					
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Toxicity	0.10	0.20	0.30	0.40	0.50	0.60

- 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

Reality

- Dose assignment complicated because p_j is unknown

	Dose Level					
	1	2	3	4	5	6
Toxicity	??	??	??	??	??	??

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	Dose Level					
	1	2	3	4	5	6
Toxicity	??	??	??	??	??	??

- We estimate p_j based on data and make decision
  - Observed toxicity rate $= \frac{t_j}{n_j} \Longrightarrow$ make decision
  - This often incorrect because of small sample size and estimation uncertainty

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	Dose Level					
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Toxicity	??	??	??	??	??	??

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    1. **Retain when current dose is above/below MTD**

Reality

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	Dose Level					
	1	2	3	4	5	6
Toxicity	??	??	??	??	??	??

- We estimate p_j based on data and make decision
  - Observed toxicity rate $= \frac{t_j}{n_j} \Longrightarrow$ 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**

Reality

- Dose assignment complicated because p_j is unknown

	Dose Level					
	1	2	3	4	5	6
Toxicity	??	??	??	??	??	??

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Reality

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	Dose Level					
	1	2	3	4	5	6
Toxicity	??	??	??	??	??	??

- We estimate p_j based on data and make decision
  - Observed toxicity rate $= \frac{t_j}{n_j} \Longrightarrow$ 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 λ_{1j} and λ_{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 λ_{1j} and λ_{2j} to minimize the decision error of dose assignment?

The optimal interval design

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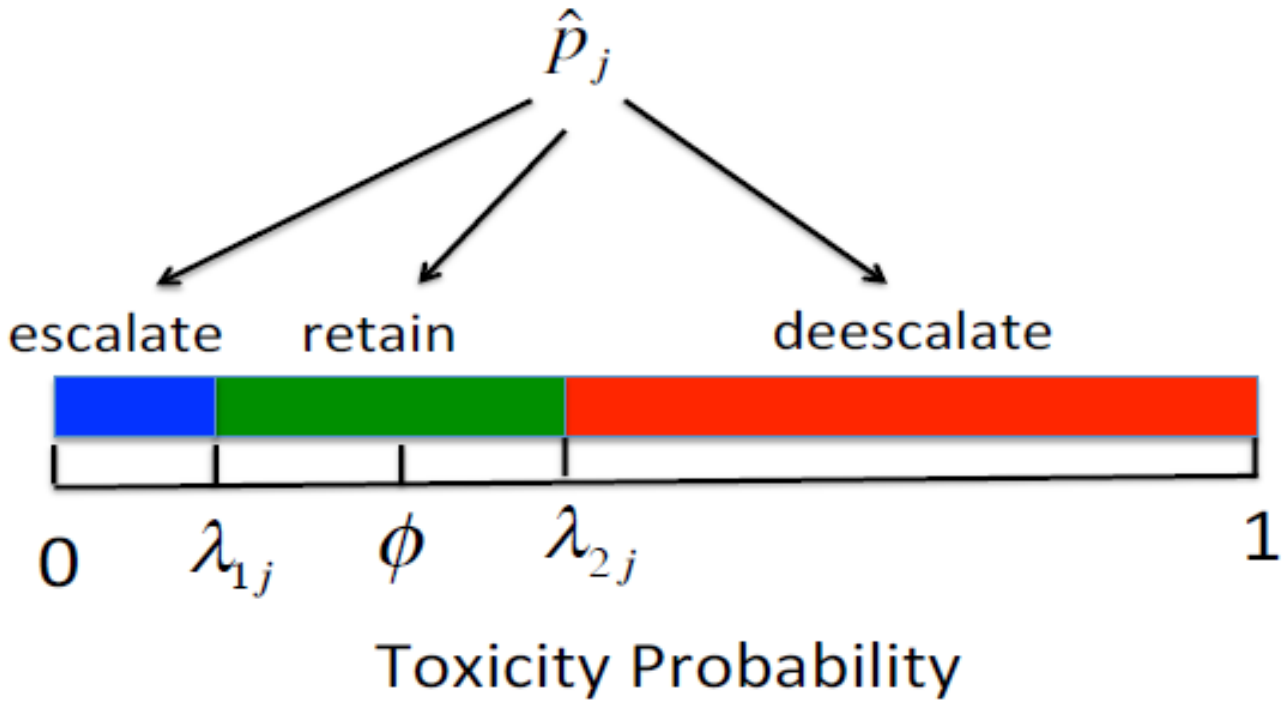

Setup

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

$$
\begin{aligned}
H_{0j}: &\quad p_j = \phi \\
H_{1j}: &\quad p_j = \phi_1 \\
H_{2j}: &\quad p_j = \phi_2
\end{aligned}
$$

Setup

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

$$\begin{aligned} H_{0j}: &\quad p_j = \phi \\ H_{1j}: &\quad p_j = \phi_1 \\ H_{2j}: &\quad p_j = \phi_2 \end{aligned}$$

- ϕ_1 denotes the highest toxicity probability deemed subtherapeutic so that dose escalation should be made
- ϕ_2 denotes the lowest toxicity probability deemed overly toxic so that dose de-escalation is required

Optimal Interval Boundaries

- 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

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

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

- The 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

Selecting the MTD

- At end of trial, based on observed data, we select the MTD dose whose isotonic estimate of toxicity rate is closest to ϕ
- 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

Stopping rule for safety

- 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

Stata syntax

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(#)
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- getboundary specifies to calculate dose escalation rules for a proposed design

Options

optinterval, getboundary selectmtd oc design(#) target(#)
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- getboundary specifies to calculate dose escalation rules for a proposed design
- selectmtd specifies to find the MTD at the end of a trial

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- getboundary specifies to calculate dose escalation rules for a proposed design
- selectmtd specifies to find the MTD at the end of a trial
- oc specifies to calculate operating characteristics for a proposed design

Options

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

- design(#) 1 specifies to use the local optimal design; 2 specifies the global optimal design; the default is 1

Options

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

- 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

optinterval, getboundary selectmtd oc design(#) target(#)
ncohort(#) cohort(#) saf(#) tox(#) cut(#)
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- target(#) specifies the target toxicity rate; this option is required and must be > 0.05 and $\leq$ 0.60
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- cohort(#) specifies the cohort size; the default is 1

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

Options

optinterval, getboundary selectmtd oc design(#) target(#)
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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—ϕ_1

Options

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

Options

optinterval, getboundary selectmtd oc design(#) target(#)
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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—ϕ_2

Options

optinterval, getboundary selectmtd oc design(#) target(#)
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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(#)
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- 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(#)
npts(*numlist*) ntox(*numlist*) startdose(#)
truep(*numlist*) ntrials(#)

- 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

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

Options

optinterval, getboundary selectmtd oc design(#) target(#)
ncohort(#) cohort(#) saf(#) tox(#) cut(#)
npts(*numlist*) ntox(*numlist*) startdose(#)
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- 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 ϕ of 0.30
- Enroll 10 cohorts in sample sizes of 3 patients
- Maximum sample size of 30 patients
- 6 doses

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)
```

Dose	1	2	3	4	5	6
Pr(Toxicity)	0.30	0.35	0.40	0.45	0.50	0.60
% Selected	47.90	22.00	11.30	2.20	1.30	0.10
Avg Toxicity	4.76	2.54	1.12	0.34	0.07	0.01
Avg Patients	16.16	7.09	2.81	0.74	0.15	0.02

```
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)
```

Dose	1	2	3	4	5	6
Pr(Toxicity)	0.10	0.20	0.30	0.40	0.50	0.60
% Selected	3.40	29.30	39.90	21.90	4.50	0.70
Avg Toxicity	0.54	1.91	2.70	1.65	0.58	0.08
Avg Patients	5.58	9.77	8.97	4.34	1.14	0.13

```
Avg Patients = 29.93
Avg Toxicities = 7.46

% Dose 1 overly toxic = .3
```

Operating Characteristics-Scenario 3

```
. optinterval, oc target(0.30) ncohort(10) cohort(3) truep(0.05 0.10 0.15 0.20 0.25 0.30) ntrials(1000)
```

Dose	1	2	3	4	5	6
Pr(Toxicity)	0.05	0.10	0.15	0.20	0.25	0.30
% Selected	0.20	2.80	10.90	21.60	30.40	34.00
Avg Toxicity	0.22	0.56	0.93	1.23	1.23	1.10
Avg Patients	3.84	5.17	6.13	6.21	4.94	3.67

```
Avg Patients = 29.98
Avg Toxicities = 5.26

% Dose 1 overly toxic = .1

.
```

Table for design write-up

		Dose Level					
		1	2	3	4	5	6
Scenario 1	Pr(tox)	0.30	0.35	0.40	0.45	0.50	0.60
	% selected	47.90	22.00	11.30	2.20	1.30	0.10
	Avg Tox	4.76	2.54	1.12	0.34	0.07	0.01
	Avg Pts	16.16	7.09	2.81	0.74	0.15	0.02
Scenario 2	Pr(tox)	0.10	0.20	0.30	0.40	0.50	0.60
	% selected	3.40	29.30	39.90	21.90	4.50	0.70
	Avg Tox	0.54	1.91	2.70	1.65	0.58	0.08
	Avg Pts	5.58	9.77	8.97	4.34	1.14	0.13
Scenario 3	Pr(tox)	0.05	0.10	0.15	0.20	0.25	0.30
	% selected	0.20	2.80	10.90	21.60	30.40	34.00
	Avg Tox	0.22	0.56	0.93	1.23	1.23	1.10
	Avg Pts	3.84	5.17	6.13	6.21	4.94	3.67

Table for design write-up

		Dose Level					
		1	2	3	4	5	6
Scenario 1	Pr(tox)	**0.30**	0.35	0.40	0.45	0.50	0.60
	% selected	**47.90**	22.00	11.30	2.20	1.30	0.10
	Avg Tox	4.76	2.54	1.12	0.34	0.07	0.01
	Avg Pts	16.16	7.09	2.81	0.74	0.15	0.02
Scenario 2	Pr(tox)	0.10	0.20	0.30	0.40	0.50	0.60
	% selected	3.40	29.30	39.90	21.90	4.50	0.70
	Avg Tox	0.54	1.91	2.70	1.65	0.58	0.08
	Avg Pts	5.58	9.77	8.97	4.34	1.14	0.13
Scenario 3	Pr(tox)	0.05	0.10	0.15	0.20	0.25	0.30
	% selected	0.20	2.80	10.90	21.60	30.40	34.00
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Table for design write-up

		Dose Level					
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Scenario 1	Pr(tox)	**0.30**	0.35	0.40	0.45	0.50	0.60
	% selected	**47.90**	22.00	11.30	2.20	1.30	0.10
	Avg Tox	4.76	2.54	1.12	0.34	0.07	0.01
	Avg Pts	16.16	7.09	2.81	0.74	0.15	0.02
Scenario 2	Pr(tox)	0.10	0.20	**0.30**	0.40	0.50	0.60
	% selected	3.40	29.30	**39.90**	21.90	4.50	0.70
	Avg Tox	0.54	1.91	2.70	1.65	0.58	0.08
	Avg Pts	5.58	9.77	8.97	4.34	1.14	0.13
Scenario 3	Pr(tox)	0.05	0.10	0.15	0.20	0.25	0.30
	% selected	0.20	2.80	10.90	21.60	30.40	34.00
	Avg Tox	0.22	0.56	0.93	1.23	1.23	1.10
	Avg Pts	3.84	5.17	6.13	6.21	4.94	3.67

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	Avg Tox	4.76	2.54	1.12	0.34	0.07	0.01
	Avg Pts	16.16	7.09	2.81	0.74	0.15	0.02
Scenario 2	Pr(tox)	0.10	0.20	**0.30**	0.40	0.50	0.60
	% selected	3.40	29.30	**39.90**	21.90	4.50	0.70
	Avg Tox	0.54	1.91	2.70	1.65	0.58	0.08
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Scenario 3	Pr(tox)	0.05	0.10	0.15	0.20	0.25	**0.30**
	% selected	0.20	2.80	10.90	21.60	30.40	**34.00**
	Avg Tox	0.22	0.56	0.93	1.23	1.23	1.10
	Avg Pts	3.84	5.17	6.13	6.21	4.94	3.67

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

         Escalate        Deescalate        Eliminate
N     (if # DLT <=)    (if # DLT >=)    (if # DLT >=)
-------------------------------------------------------
3             0                2                3
6             1                3                4
9             2                4                5
12            2                5                7
15            3                6                8
18            4                7                9
21            4                8                10
24            5                9                11
27            6                10               12
30            7                11               14
```

Decision Boundaries–design write-up

Decision	# of Patients Treated at Current Dose Level									
	3	6	9	12	15	18	21	24	27	30
Escalate if # DLT $\leq$	0	1	2	2	3	4	4	5	6	7
De-escalate if # DLT $\geq$	2	3	4	5	6	7	8	9	10	11
Eliminate if # DLT $\geq$	3	4	5	7	8	9	10	11	12	14

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

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1. Cohort 1 (1/3) $\rightarrow$ Retain Dose 1

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

1. Cohort 1 (1/3) $\rightarrow$ Retain Dose 1
2. Cohort 2 (1/6) $\rightarrow$ Escalate to Dose 2

Decision Boundaries–design write-up

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De-escalate if # DLT $\geq$	2	3	4	5	6	7	8	9	10	11
Eliminate if # DLT $\geq$	3	4	5	7	8	9	10	11	12	14

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

1. Cohort 1 (1/3) $\rightarrow$ Retain Dose 1
2. Cohort 2 (1/6) $\rightarrow$ Escalate to Dose 2
3. Cohort 3 (2/3) $\rightarrow$ De-escalate to Dose 1

Decision Boundaries–design write-up

Decision	# of Patients Treated at Current Dose Level									
	3	6	9	12	15	18	21	24	27	30
Escalate if # DLT $\leq$	0	1	2	2	3	4	4	5	6	7
De-escalate if # DLT $\geq$	2	3	4	5	6	7	8	9	10	11
Eliminate if # DLT $\geq$	3	4	5	7	8	9	10	11	12	14

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

1. Cohort 1 (1/3) $\rightarrow$ Retain Dose 1
2. Cohort 2 (1/6) $\rightarrow$ Escalate to Dose 2
3. Cohort 3 (2/3) $\rightarrow$ De-escalate to Dose 1
4. Cohort 4 (2/9) $\rightarrow$ Escalate to Dose 2

Decision Boundaries–design write-up

Decision	# of Patients Treated at Current Dose Level									
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4. Cohort 4 (2/9) $\rightarrow$ Escalate to Dose 2
5. Cohort 5 (2/6) $\rightarrow$ Retain Dose 2

Decision Boundaries–design write-up

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

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3. Cohort 3 (2/3) $\rightarrow$ De-escalate to Dose 1
4. Cohort 4 (2/9) $\rightarrow$ Escalate to Dose 2
5. Cohort 5 (2/6) $\rightarrow$ 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

References

Liu, S. and Yuan, Y. 2013 Bayesian Decision-optimal Interval Designs for Phase I Clinical Trials, Journal of the Royal Statistical Society: Series C, revision invited

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 ϕ (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

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, escalation, and de-escalation of the current dose level
- The incorrect decisions under H_0, H_1, and H_2 are $\widetilde{\mathcal{R}}$, $\widetilde{\mathcal{E}}$, and $\widetilde{\mathcal{D}}$, respectively, where $\widetilde{\mathcal{R}}$, $\widetilde{\mathcal{E}}$, and $\widetilde{\mathcal{D}}$ denote the decisions complementary to $\mathcal{R}$, $\mathcal{E}$, and $\mathcal{D}$

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:

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

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\alpha &\equiv \text{Pr(incorrect decision)} \\
&= Pr(H_0)Pr(\widetilde{\mathcal{R}}|H_0) + Pr(H_1)Pr(\widetilde{\mathcal{E}}|H_1) + Pr(H_2)Pr(\widetilde{\mathcal{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) \\
&\quad + Pr(H_2)Pr(\hat{p}_j < \lambda_{2j}|H_2)
\end{aligned}$$

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:

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

Theorem 1–λ_{1j} and λ_{2j}

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

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

This provides intuitive justification for escalation/de-escalation rules!!

Theorem 2–Finite-sample property: coherence

- 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 ϕ

Theorem 3–Large-sample property: convergence

- 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 does 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