The Joint i3+3 (Ji3+3) Design for Phase I Dose-finding Trials

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Outline

Introduction - Phase I Dose-finding Trials & Statistical Design

Original i3+3 - Method & Motivation

Joint i3+3 - Motivation, Method, Operating Characteristics

Phase I Dose-Finding Trials

Phase I studies are often designed to find the "best" dose in human

How one defines "best" will be one of the primary factors in study design

- Typically, "best" is defined as the dose where the probability of toxic event (DLT), is less than some pre-determined threshold
- MTD (maximum tolerable dose)
- Assumption: monotonic dose-response curve ("tolerance distribution") in toxicity setting

Statistical Methods for Phase I Trials

- 3+3
  - Model free, widely used
- Continual re-assessment method (CRM) based
  - $Pr(DLT = 1 \mid dose = x) = \Psi(x, \boldsymbol{a})$, continuous, monotone function of dose $0 \leq x \leq \infty$
- Bayesian Logistic Regression Modeling (BLRM)
  - $logit\{\pi_\theta(d)\} = \log \alpha + \beta \log(\frac{d}{d^\star})$, $\alpha, \beta > 0$
- Interval-based designs - mTPI, mTPI-2, BOIN, Keyboard
  - $(0, p_T - \epsilon_1), [p_T - \epsilon_1, p_T + \epsilon_2], (p_T + \epsilon_2, 1)$

The "Original" i3+3 Design

- $d = 1, ..., D$ ascending doses to be tested
- target toxicity rate p_T and equivalence interval (EI) $[p_T - \epsilon_1, p_T + \epsilon_2]$
- x_d: number of observed DLTs at dose d; n_d: number of patients treated at dose d

Dose escalation rule by "i3+3"

Condition	Next dose level
$\frac{x}{n}$ below EI	$d+1$
$\frac{x}{n}$ inside EI	d
$\frac{x}{n}$ above EI and $\frac{x-1}{n}$ below EI	d
$\frac{x}{n}$ above EI and $\frac{x-1}{n}$ inside EI	$d-1$
$\frac{x}{n}$ above EI and $\frac{x-1}{n}$ above EI	$d-1$

An Intuitive Example for "i3+3"

Suppose $p_T = 0.3$ with $EI = [0.25, 0.35]$

- Suppose $x_d = 3$ and $n_d = 6$
- mTPI design assigns "S" (stay at dose d) for the next cohort of patients
- In practice, "D" is considered safer and more desirable
- This type of argument has been raised by IRB review committee and regulatory agencies
- Actually, no consensus on what decisions are acceptable in real world trials
- Depends on review committee's experiences, preference, and common sense
  - $x_d = 3$ out of $n_d = 3$?
  - $x_d = 1$ out of $n_d = 3$?
  - $x_d = 3$ out of $n_d = 6$?

An Intuitive Example for "i3+3"

- It is widely accepted that the optimal decision is "S" when $x_d = 1$ out of $n_d = 3$ for 3+3 design
- However, "S" when $x_d = 3$ out of $n_d = 6$ is deemed too risky

Sample size (or data variability) plays the role

- For $x_d = 1, n_d = 3$ in 3+3 design, although $\frac{1}{3}$ is twice higher than the target rate $\frac{1}{6}$, the sample size $n_d = 3$ is too small to distinguish between $\frac{1}{3}$ and $\frac{1}{6}$; with 1 fewer DLT, $\frac{0}{3}$ is below $\frac{1}{6}$
- For $x_d = 3, n_d = 6$ in mTPI design, $\frac{3}{6}$ is higher than the target 0.3, and with 1 fewer DLT, $\frac{2}{6}$ is still higher than 0.3
- In summary, $\frac{3}{6}$ is more informative than $\frac{1}{3}$

Motivation for Joint i3+3 Design

For cytotoxic agent or chemo-therapy, monotonic dose-response is assumed

- Toxicity increases with dose
- Efficacy increases with dose

For immunotherapy, Adoptive cell therapy or gene therapy

- Monotonic dose-response can be assumed for toxicity, but not efficacy
- Efficacy may increase to a plateau or decrease with dose
- Optimal dose $\neq$ MTD
  - balance immune system boosting = combat cancer cells + avoiding over-stimulation

Feasibility of Joint i3+3 Design

For hematologic trials

- relatively easy to assess both toxicity and efficacy endpoints within reasonable time limits
- Usually within 8 weeks

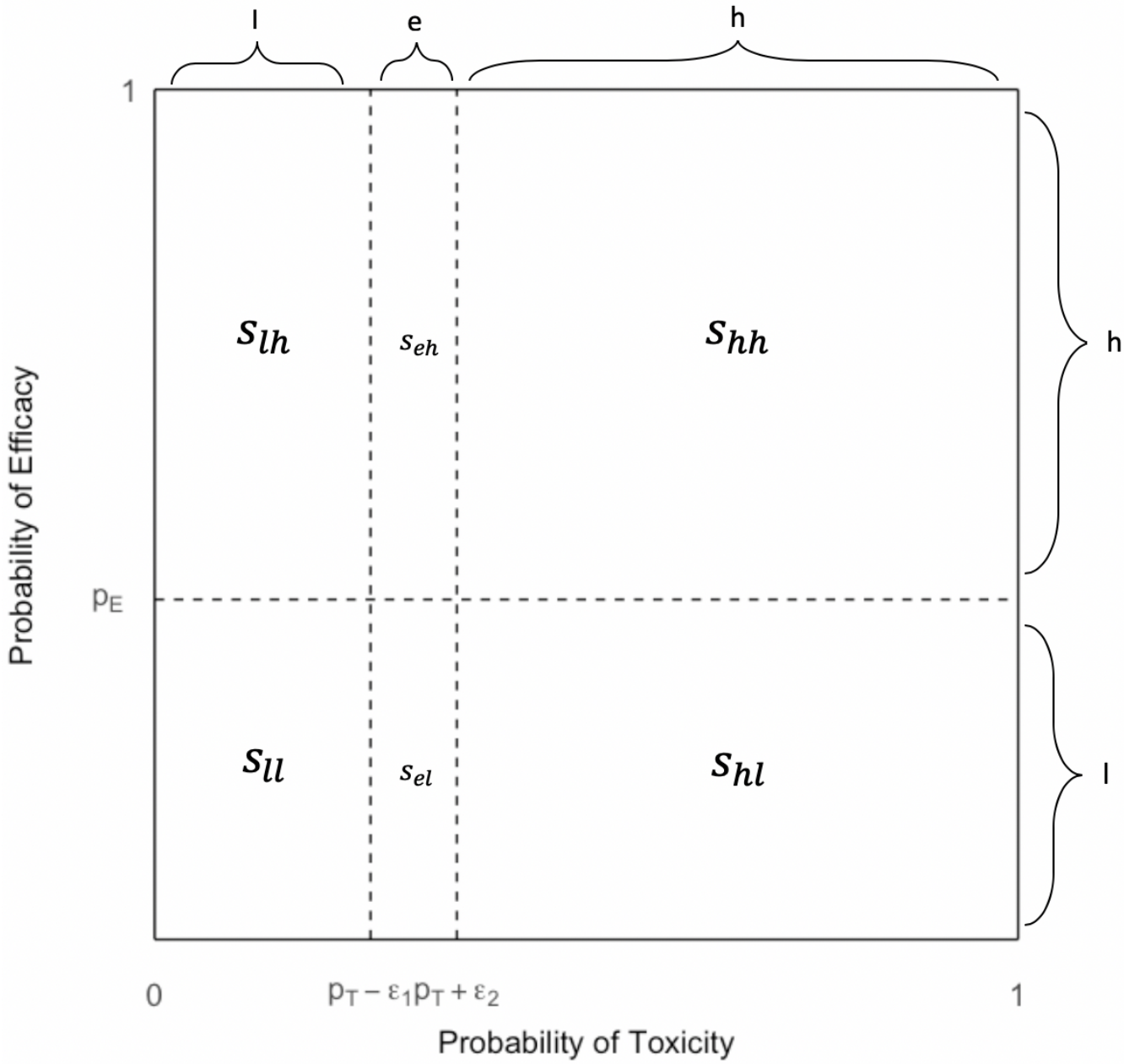
For solid tumor trials

- Can be difficult to assess efficacy outcomes quickly
- Time-to-event design is being developed for the jointly modeling of toxicity and efficacy within the i3+3 framework

Design Set-up

- $d = 1, ..., D$: ascending dose levels
- p_d, q_d: true probabilities of toxicity and efficacy at dose d
  - $p_1 \leq ... \leq p_D$
  - no ordering assumed for $q_1, ..., q_D$
- x_d, y_d, n_d: observed DLT, efficacy outcomes and patients treated at dose level d
- p_T, (ϵ_1, ϵ_2): target toxicity rate, small proportions
  - Equivalence toxicity interval: $EI = [p_T - \epsilon_1, p_T + \epsilon_2]$
  - Under dosing toxicity interval: $UI = (0, p_T - \epsilon_1)$
  - Over dosing toxicity interval: $OI = (p_T + \epsilon_2, 1)$
- p_E: efficacy threshold
  - Insufficient efficacy: $(0, p_E)$
  - Sufficient efficacy: $[p_E, 1)$

Probability Region: $S_{tox,eff}$



Dose-finding Algorithm

Current dose d; n_d patients, x_d Tox, y_d Eff		
Eff cond.	Tox cond.	Next dose (Decision)
$\frac{y_d}{n_d} \leq p_E$	$\frac{x_d}{n_d} < \text{EI}$	$d+1$ (E)
	$\frac{x_d}{n_d} \in \text{EI}$	$d+1$ (E)
	$\frac{x_d}{n_d} > \text{EI}$ & $\frac{x_d-1}{n_d} < \text{EI}$	d (S)
	$\frac{x_d}{n_d} > \text{EI}$ & $\frac{x_d-1}{n_d} \in \text{EI}$	$d-1$ (D)
	$\frac{x_d}{n_d} > \text{EI}$ & $\frac{x_d-1}{n_d} > \text{EI}$	$d-1$ (D)
$\frac{y_d}{n_d} > p_E$	$\frac{x_d}{n_d} < \text{EI}$	d (S)
	$\frac{x_d}{n_d} \in \text{EI}$	d (S)
	$\frac{x_d}{n_d} > \text{EI}$ & $\frac{x_d-1}{n_d} < \text{EI}$	d (S)
	$\frac{x_d}{n_d} > \text{EI}$ & $\frac{x_d-1}{n_d} \in \text{EI}$	$d-1$ (D)
	$\frac{x_d}{n_d} > \text{EI}$ & $\frac{x_d-1}{n_d} > \text{EI}$	$d-1$ (D)

Terminal Rules

- If the current dose is the highest dose, decision escalate “E” should be replaced with decision stay “S”, since there is no dose to escalate to.
- Similarly, if the current dose is the lowest dose, decision de-escalate “D” should be replaced with stay “S” since there is no dose to de-escalate to.

Safety & Futility Rules

- Safety rule: if $Pr(p_d > p_T \mid x_d, n_d) > \eta$ for a η close to 1 (say, 0.95), exclude doses $d, d+1, ..., D$, from future use in this trial and treat the next cohort of patients at dose $(d-1)$.

- Futility rule: if $Pr(q_d > q_E \mid y_d, n_d) < \epsilon$ for a small ϵ (say, 0.3), where q_E is the minimum acceptable probability of efficacy, then exclude dose d from future use in the trial. Note that usually $q_E < p_E$ which is considered as a lower bound efficacy rate to justify the test of the drug in a trial.

Pre-calculated Decision Table

# of pats. at current dose	Toxicity counts	Efficacy counts		
		0-1	2-3	
3	0-1	E	S	
	2	D	D	
	3	DU_T	DU_T	
		0	1-2	3-6
6	0-2	EU	E	S
	3	DU_E	D	D
	4-6	DU_T	DU_T	DU_T
		0	1-3	4-9
9	0-3	EU	E	S
	4	DU_E	D	D
	6-9	DU_T	DU_T	DU_T
		0-1	2-4	5-12
12	0-4	EU	E	S
	5-6	DU_E	D	D
	7-12	DU_T	DU_T	DU_T
		0-1	2-6	7-15
15	0-5	EU	E	S
	6-7	DU_E	D	D
	8-15	DU_T	DU_T	DU_T

Final Dose Selection

At the end of the trial, BOD (Biological Optimal Dose) is selected among multiple candidate doses based on joint utility scores $U(p, q) = f_1(p)f_2(q)$

- For toxicity,

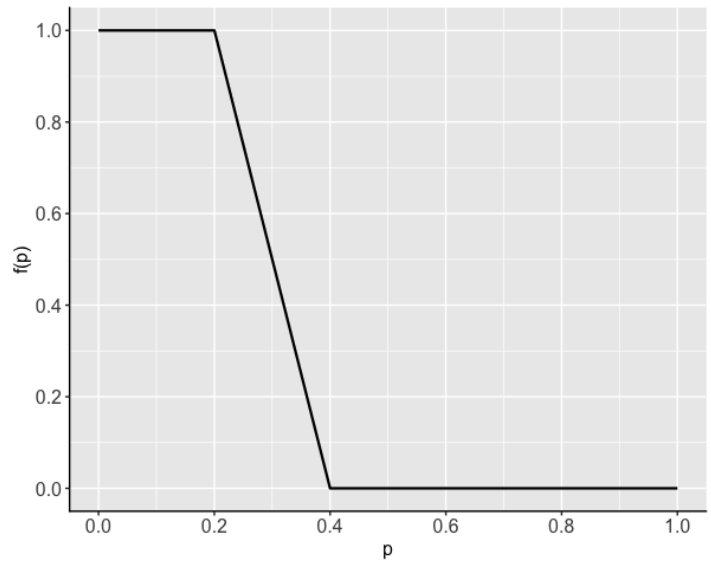
$$f_1(p) = \begin{cases} 1, & p \in (0, p_1^\star). \\ 1 - \frac{p - p_1^\star}{p_2^\star - p_1^\star} & p \in (p_1^\star, p_2^\star), \\ 0, & p \in (p_2^\star, 1) \end{cases}$$

- For efficacy,

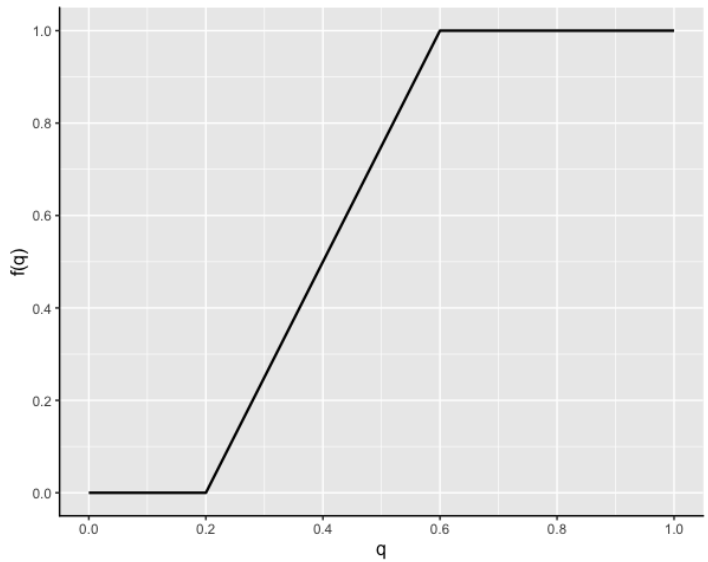
$$f_2(q) = \begin{cases} 0, & q \in (0, q_1^\star). \\ \frac{q - q_1^\star}{q_2^\star - q_1^\star} & q \in (q_1^\star, q_2^\star), \\ 1, & q \in (q_2^\star, 1) \end{cases}$$

Utility Functions

Suppose $p_T = 0.3$, $(p_1^\star, p_2^\star) = (0.2, 0.4)$, $(q_1^\star, q_2^\star) = (0.2, 0.6)$



(a) Safety utility function



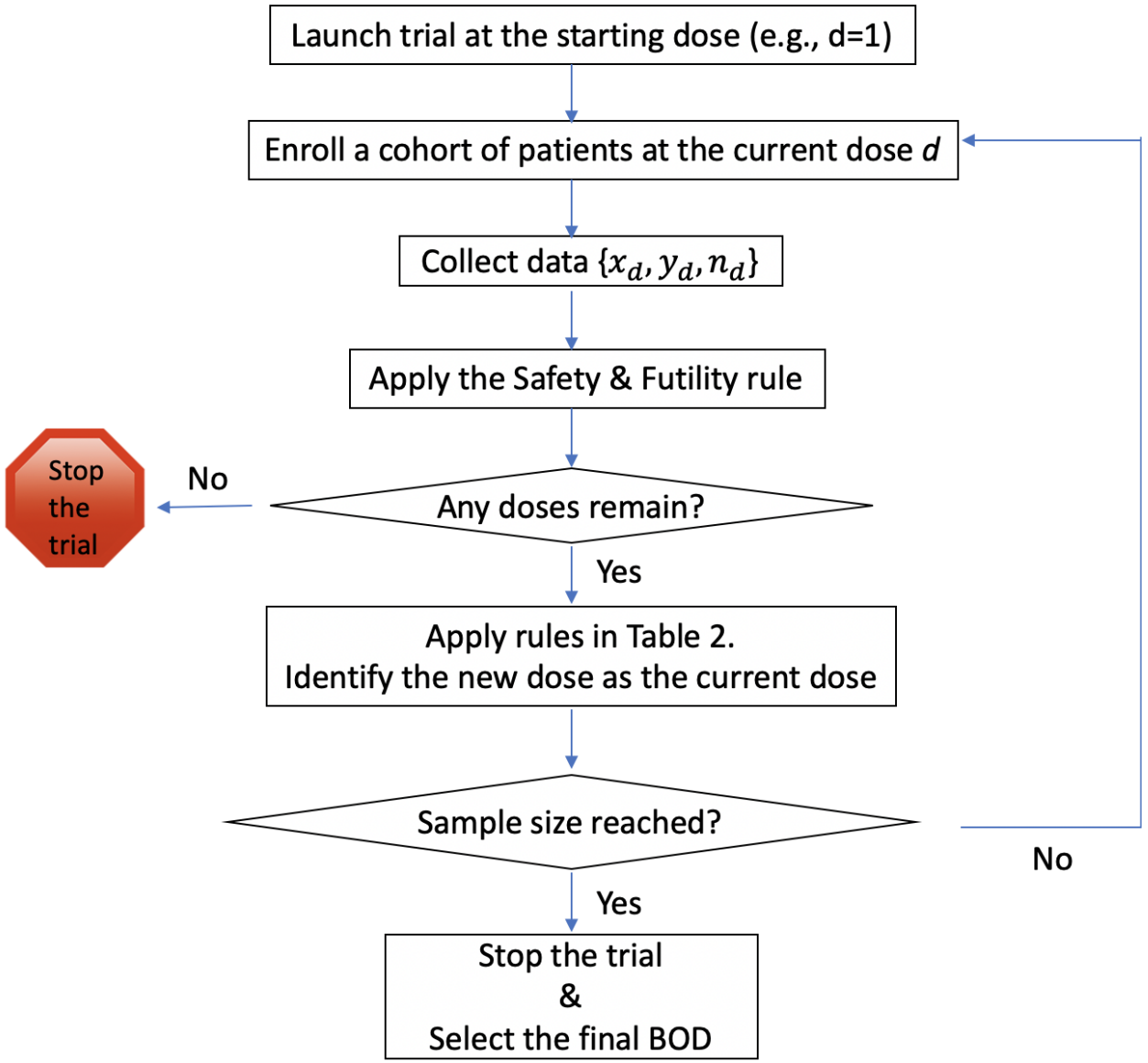
(b) Efficacy utility function

BOD Filtering

The joint utility score for the final selected BOD might be low and not statistically distinguishable from 0, therefore, we propose a probabilistic inference for BOD filtering

- $A(p,q) = \{(p,q) \mid p \in (0, p_T], q \in [q_E + \delta, 1)\}$: Admissible probability region (APR)
  - q_E: minimal accepted efficacy rate
  - δ: minimal accepted clinical difference from the standard of care
- $B = \{U(p,q), (p,q) \in A(p,q)\}$: admissible utility region
- For the selected dose d, calculate $p_{in} = Pr(U(p_d, q_d) \in B \mid data)$
  - If p_{in} is below some threshold $p_{graduate}$, no BOD will be selected
  - otherwise, d will be selected as the BOD

Trial Conduct

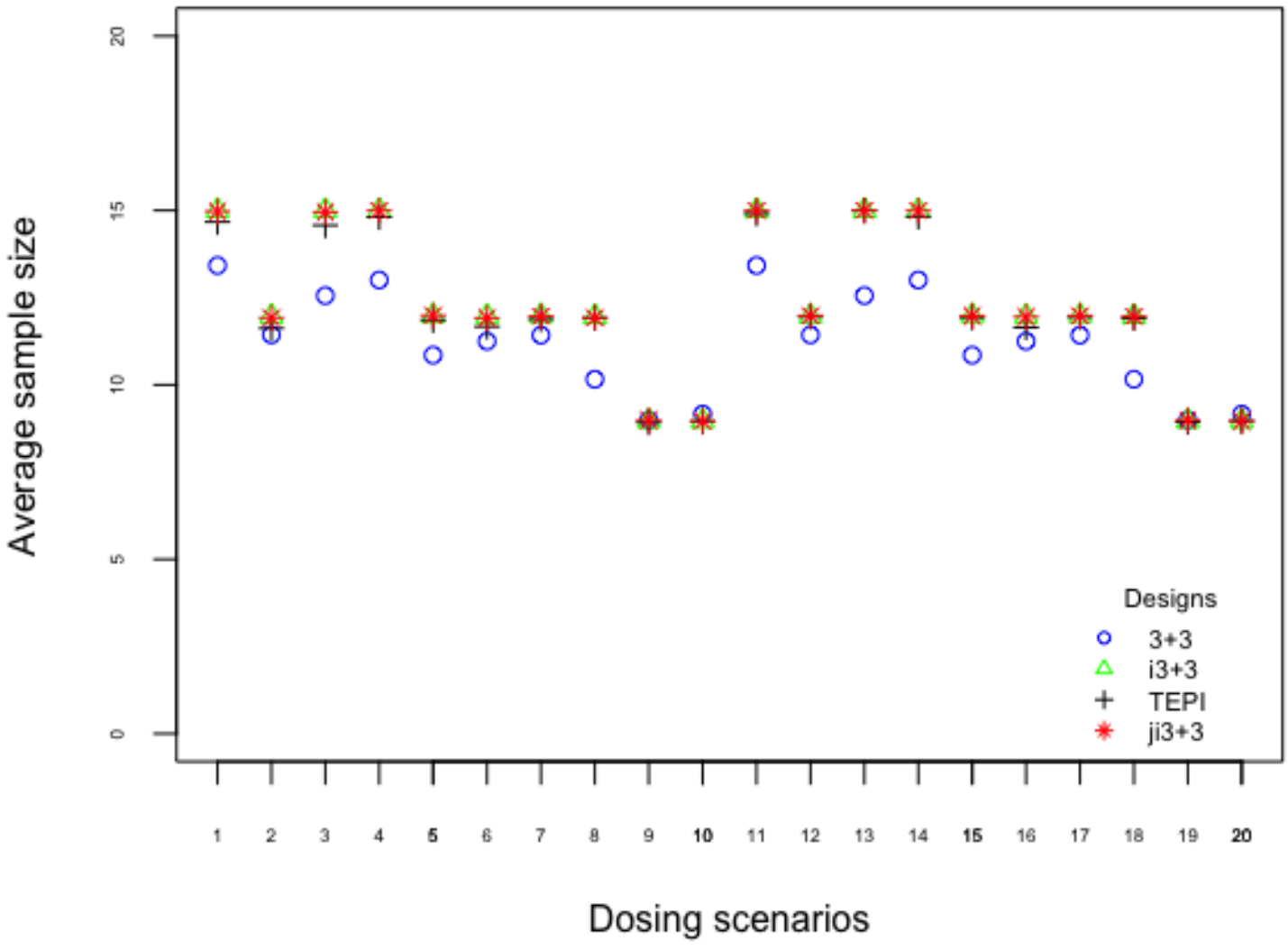


Operating Characteristics

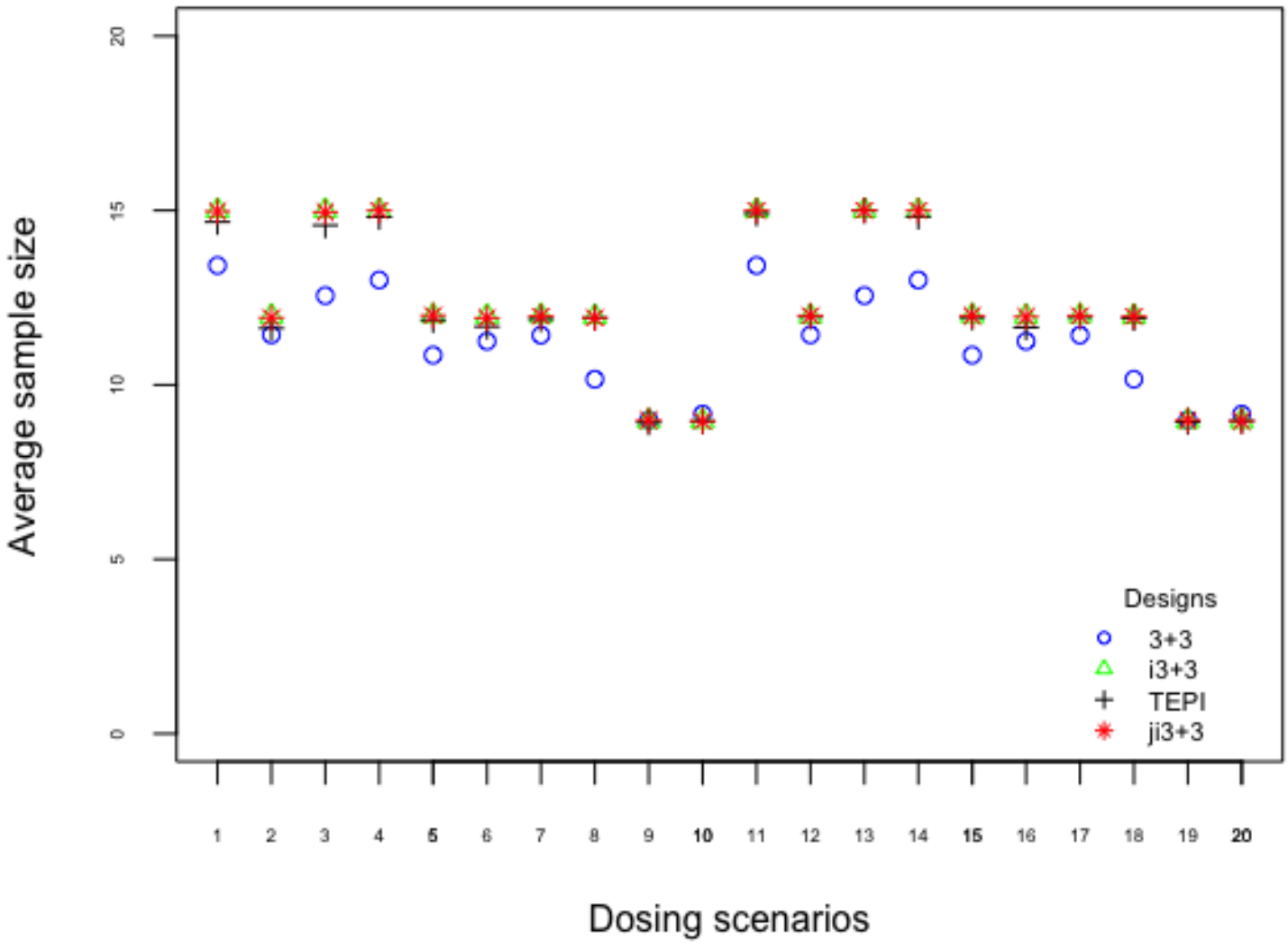
Simulation set-up

- A total of 1000 trials simulated under 20 dosing scenarios
  - scenario 1- 10 : monotonic dose-toxicity and dose-efficacy
  - scenario 11-20: monotonic dose toxicity, no-monotonic dose-efficacy
- 4 dose levels ($D = 4$)
- Design methods: 3+3, i3+3, Ji3+3, TEPI
- Sample size are matched by 3+3

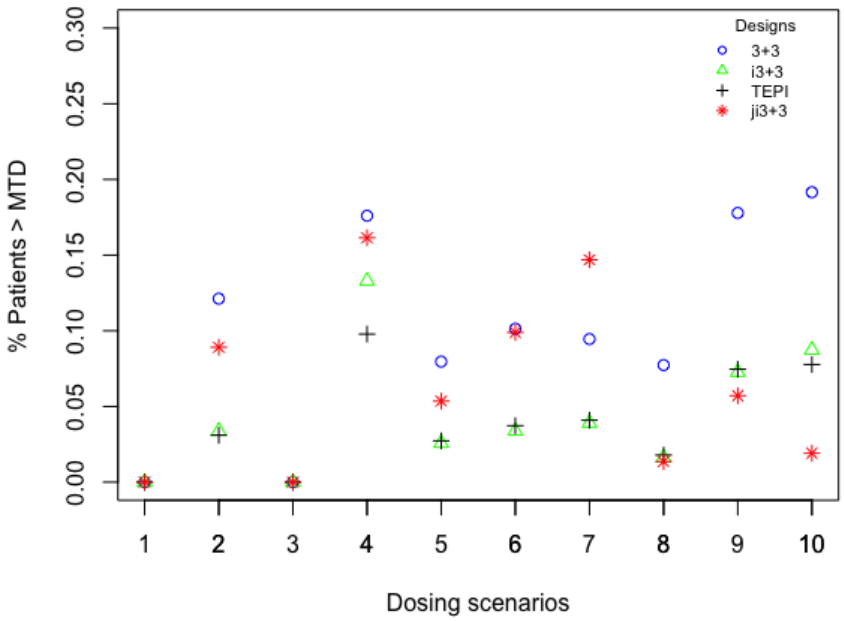
Average Sample Size



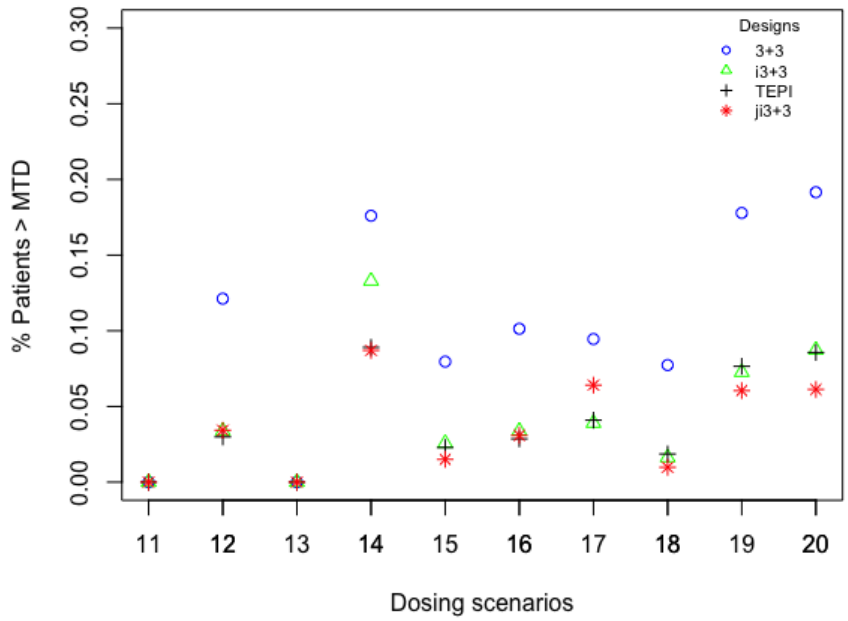
Average Sample Size



Safety


Designs
3+3
i3+3
TEPI
ji3+3
% Patients > MTD
0.00
0.05
0.10
0.15
0.20
0.25
0.30
1
2
3
4
5
6
7
8
9
10
Dosing scenarios

(c)


Designs
3+3
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0.00
0.05
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0.15
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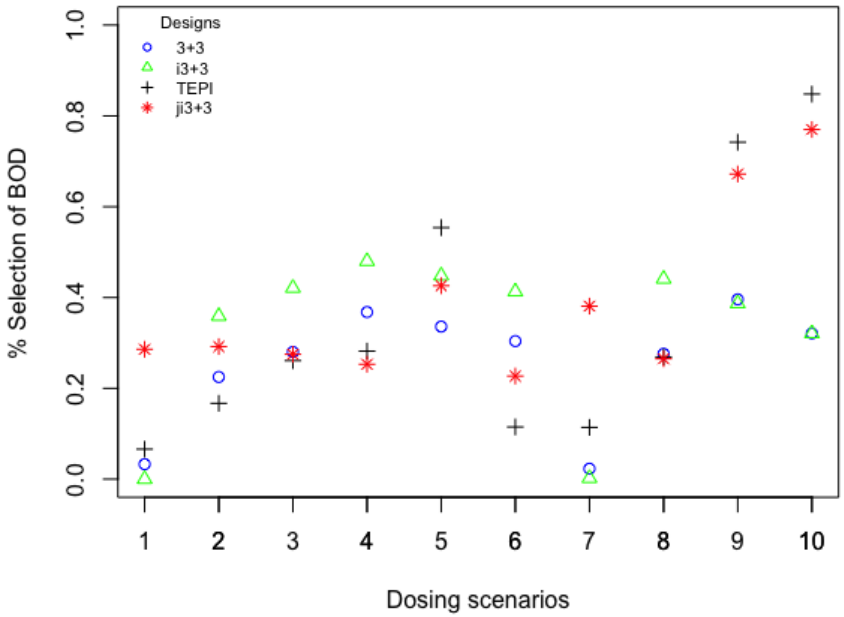
Dosing scenarios

(d)

Reliability



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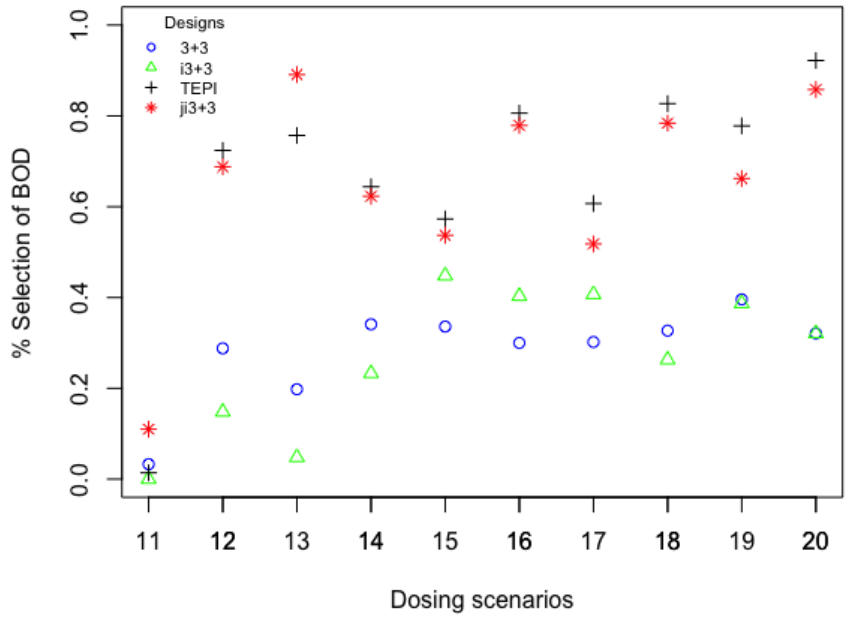
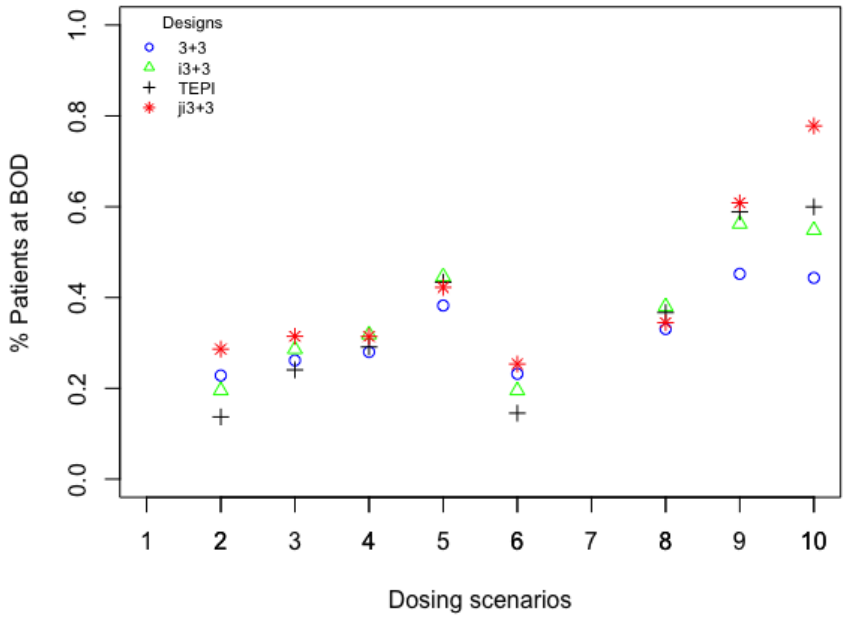
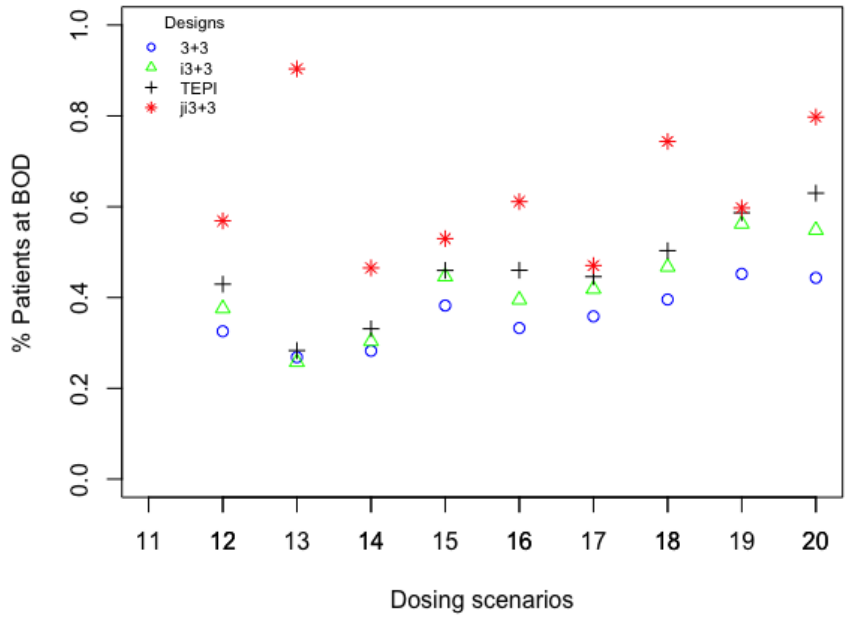


(f)

Desirability



(g)



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Summary

Ji3+3

- "model free" and rule based
- takes into account of both toxicity and efficacy data
- recommended for trials with non-monotonic dose response relationship
- Novel BOD filtering mechanism with APR and AUR
- Improve TEPI by a simplified rule based dose escalation algorithm without decreasing the operating characteristics

Challenge

Assessment window for efficacy endpoints

- might be > 12 weeks for solid tumors
- Surrogate endpoint
- Time-to-event modeling for efficacy endpoints

Elicitation for design parameters

- p_T, (ϵ_1, ϵ_2) elicited by physicians
- p_E needs to be calibrated for each trials
- q_E and δ follows a phase II convention

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Thank You for listening
Any Question!
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