# Statistical Designs for Early Phase Oncology Drug Development in the Era of Dose Optimizing for Targeted Therapeutics

Yuan Ji, PhD

Professor of Biostatistics

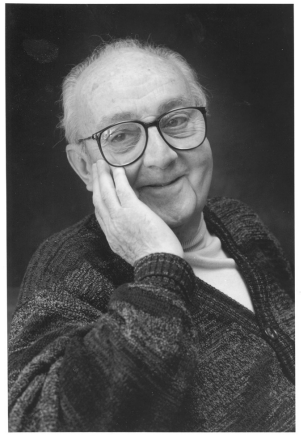
The University of Chicago

# Conflict of Interests

- U-Design is a commercial platform developed by Laiya Consulting, Inc., now part of Cytel Inc., called “East Bayes”
- Yuan Ji is a co-founder of Bayesoft
  - Also, an IDMC member for Astellas and BI
  - Executive Advisor for Cytel
  - Research contracts with Pfizer

All models are wrong, but some are useful.

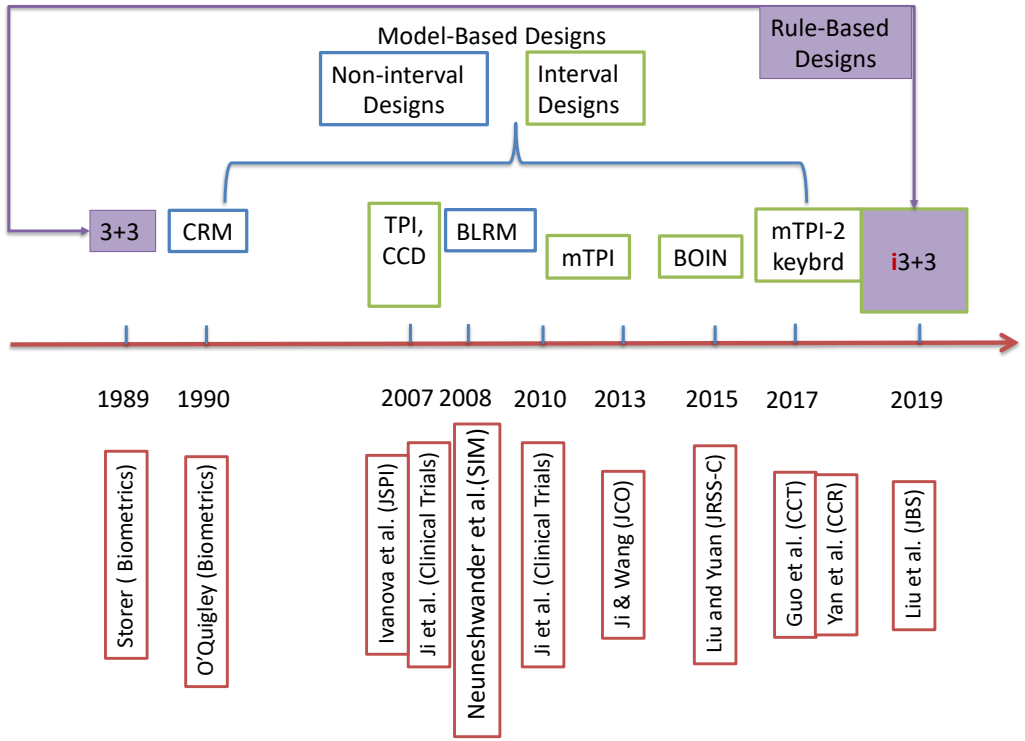
-- George Box

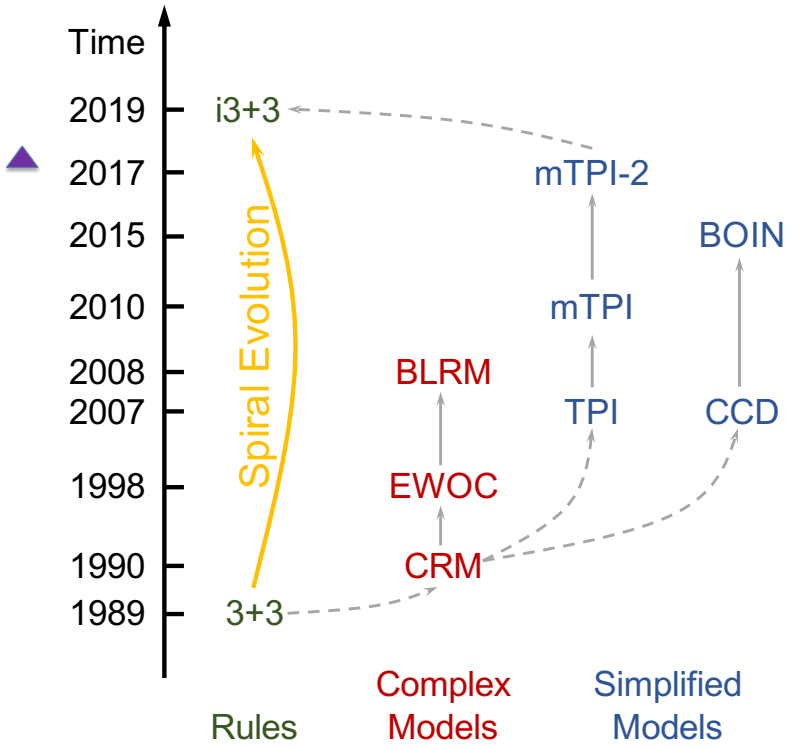


(1919-2013)

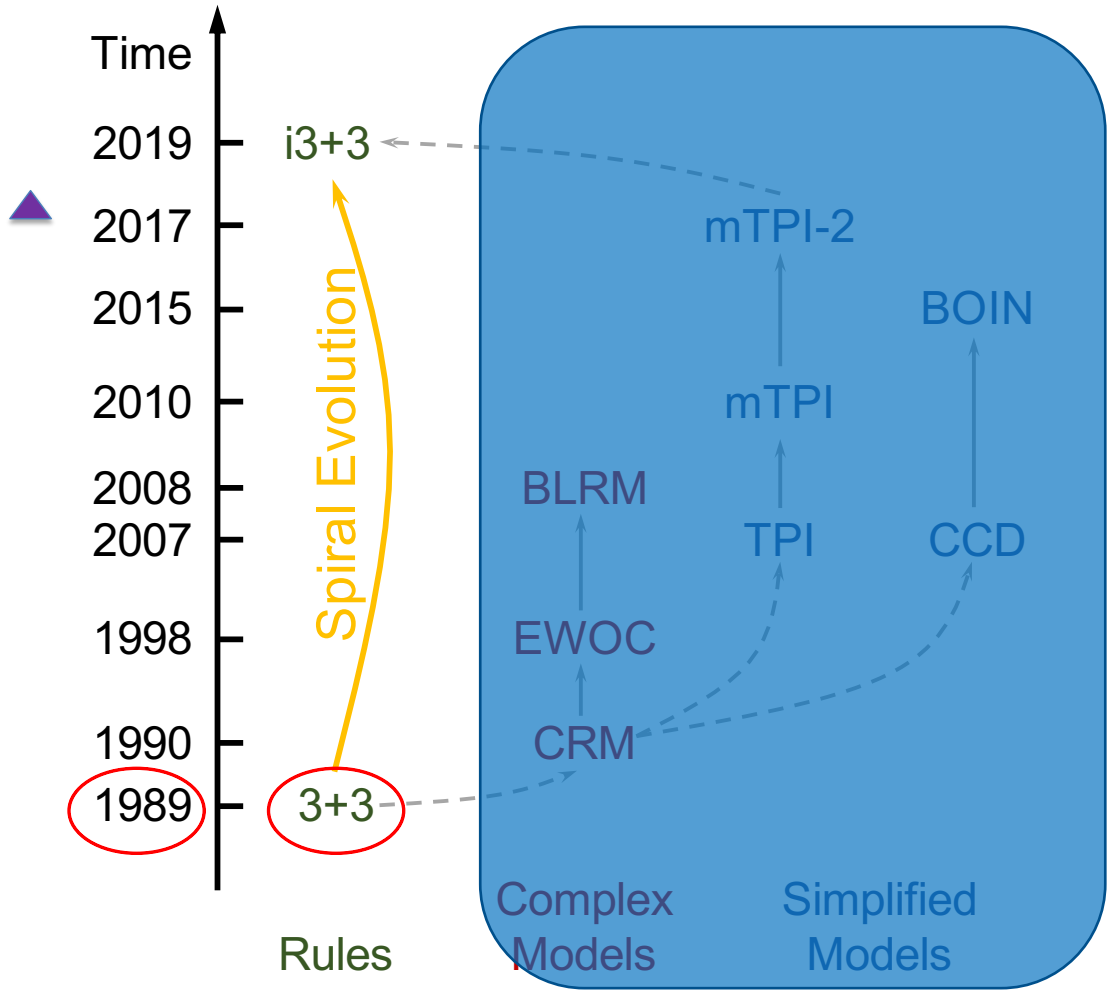
# Dose-finding designs over last 30 years

- So many designs are available now. Which one to use?

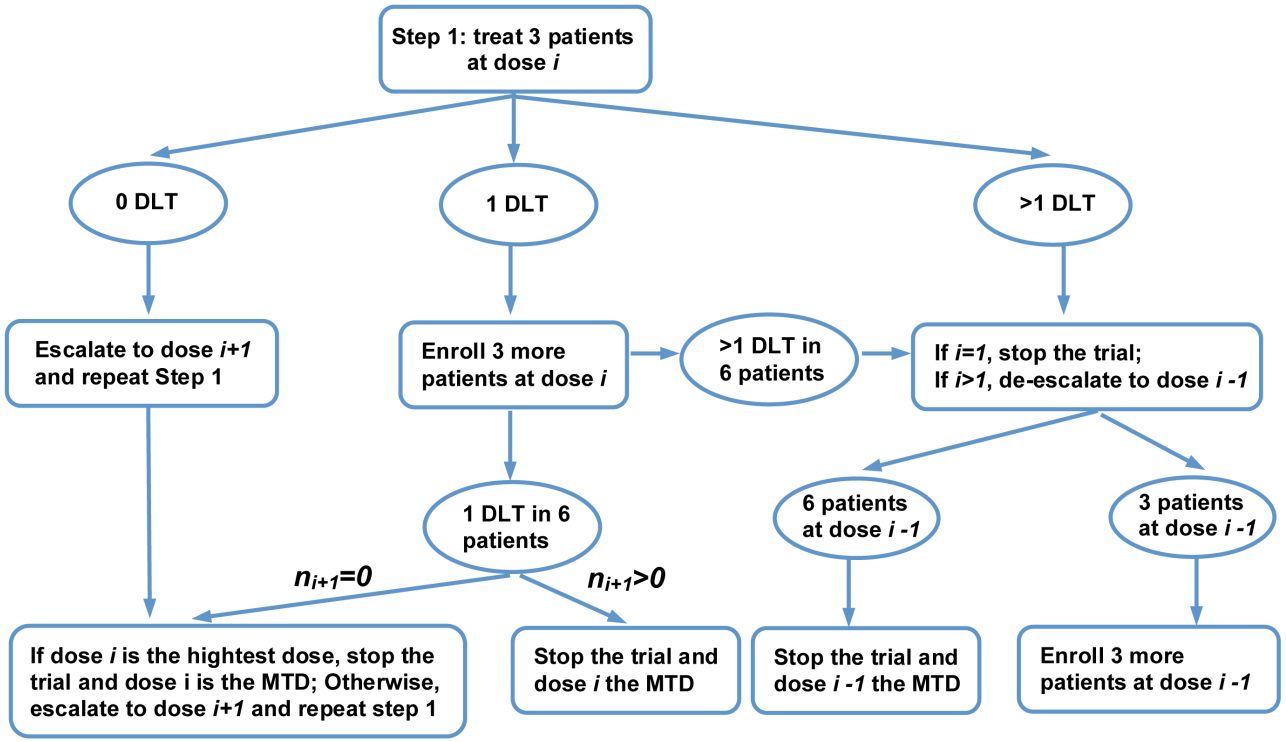


# The 3+3 design (1989)



# The 3+3 design (1989)




- Rule based
- No statistical models
  - Easy
  - Transparent
  - Societal acceptance
- Naïve/Rigid
  - <= 6 patients per dose
  - MTD wide range (1/6-1/3)
  - Performance depends on the # of doses
  - Large variabilities in MTD identification
  - Often little data supporting RP2D choices

# Numerous papers have shown 3+3 is inferior in many ways

J Clin Oncol. 2013 May 10;31(14):1785-91. doi: 10.1200/JCO.2012.45.7903. Epub 2013 Apr 8.

## Modified toxicity probability interval design: a safer and more reliable method than the 3 + 3 design for practical phase I trials

Yuan Ji [1], Sue-Jane Wang

Affiliations + expand

PMID: 23569307 PMCID: PMC3641699 DOI: 10.1200/JCO.2012.45.7903

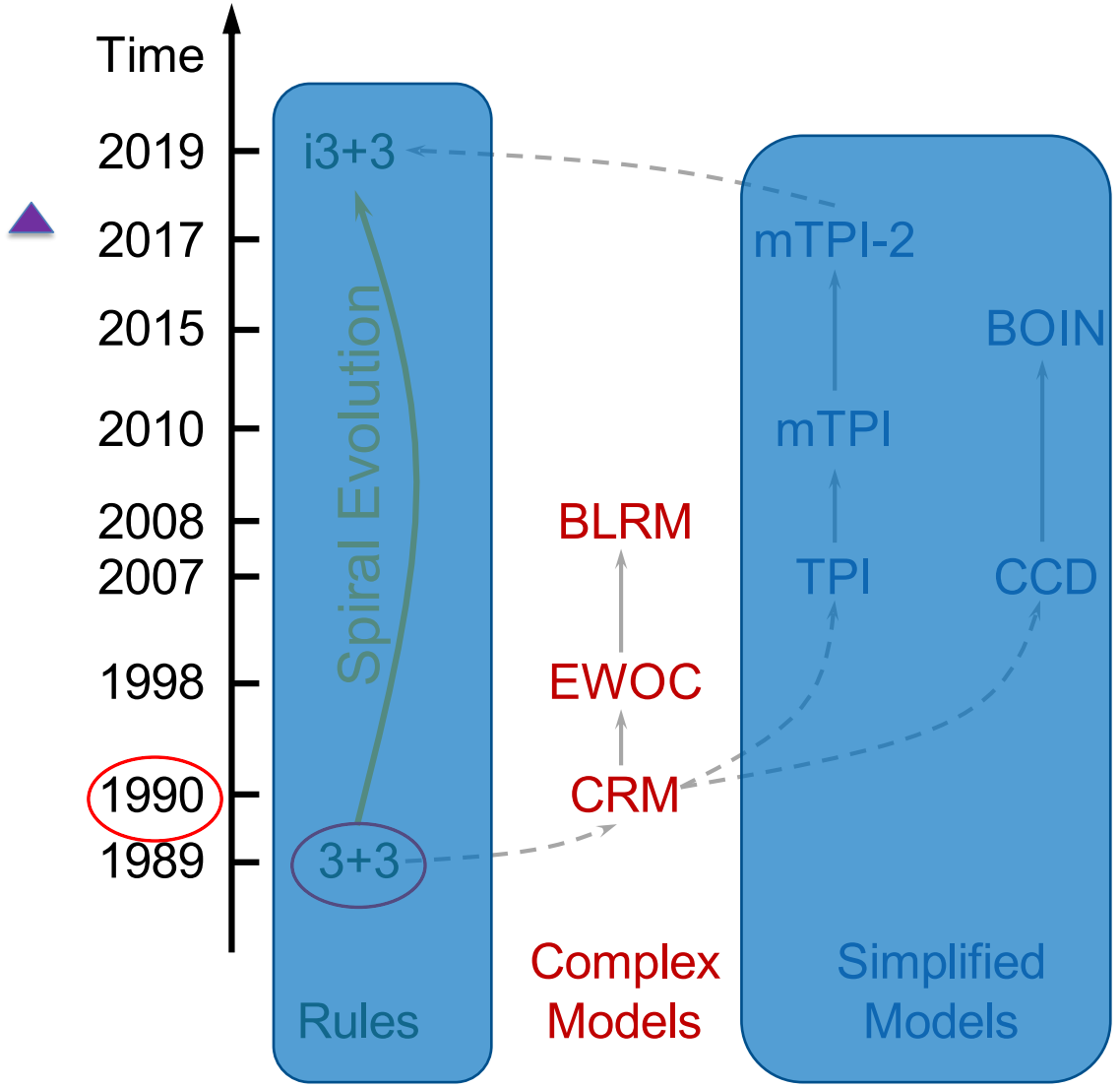
Free PMC article

CCR FOCUS 2016

## Rendering the 3 + 3 Design to Rest: More Efficient Approaches to Oncology Dose-Finding Trials in the Era of Targeted Therapy

Lei Nie[1], Eric H. Rubin[2], Nitin Mehrotra[3], José Pinheiro[4], Laura L. Fernandes[1], Amit Roy[5], Stuart Bailey[6], and Dinesh P. de Alwis[7]

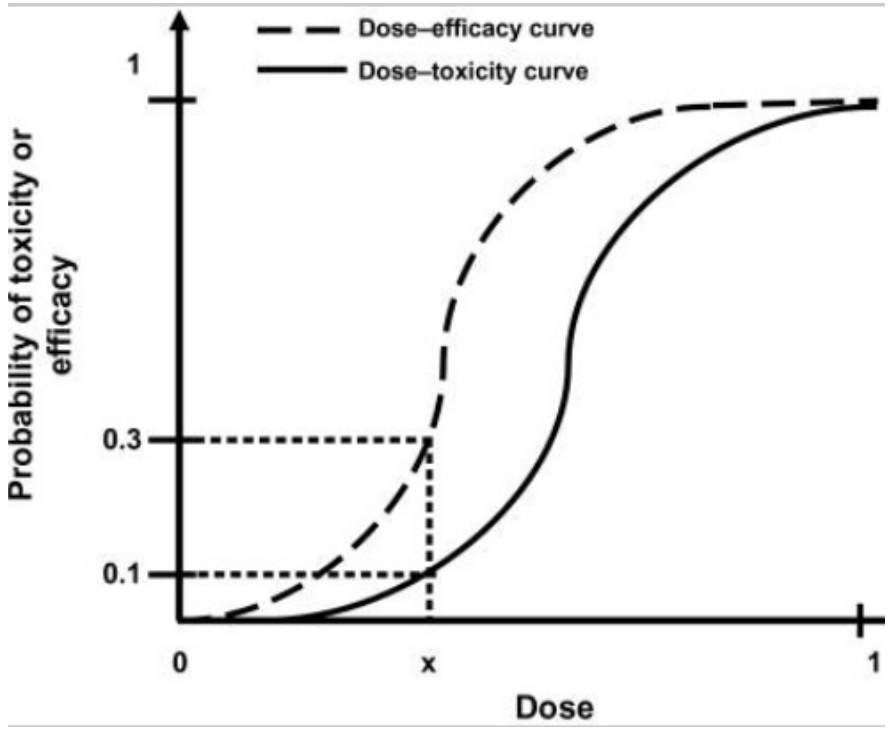
# The CRM designs (1990-2007)



# The CRM & BLRM designs

- MTD: a target rate $p_T$
- BLRM: probability intervals
- Dose-response curve
- $p(x) = p_0(x)^{\exp(\alpha)}$ or $\text{logit}^{(-1)}(x\beta)$
  - $\alpha \sim N(0, 1.34)$; or $\beta \sim prior$
  - $p_0(x)$ is the "skeleton"
  - Next dose = argmin$|\hat{p}(x) - p_T|$ or based on posterior prob. of intervals
- Operation
  - Need a statistical expert for inference and decision making
  - Too complex for the clinical team
  - SMC may override dosing decision
  - Ad-hoc rules for over-dose control

- Model based
  - Account for variability
  - Dose response curves
  - Flexible and powerful
- Lots of modifications
  - Over-dose control
  - Bayesian models
  - # of parameters
  - Black box, complex, costly



Wheeler *et al. BMC Medical Research Methodology* (2019) 19:18
https://doi.org/10.1186/s12874-018-0638-z

BMC Medical Research Methodology

TECHNICAL ADVANCE Open Access

# How to design a dose-finding study using the continual reassessment method

Graham M. Wheeler[1*], Adrian P. Mander[2], Alun Bedding[3], Kristian Brock[4], Victoria Cornelius[5], Andrew P. Grieve[6], Thomas Jaki[7], Sharon B. Love[8,9], Lang'o Odondi[8], Christopher J. Weir[10], Christina Yap[4] and Simon J. Bond[2,11]

Hundreds of papers on CRM over the past 3 decades – very popular as a research topic

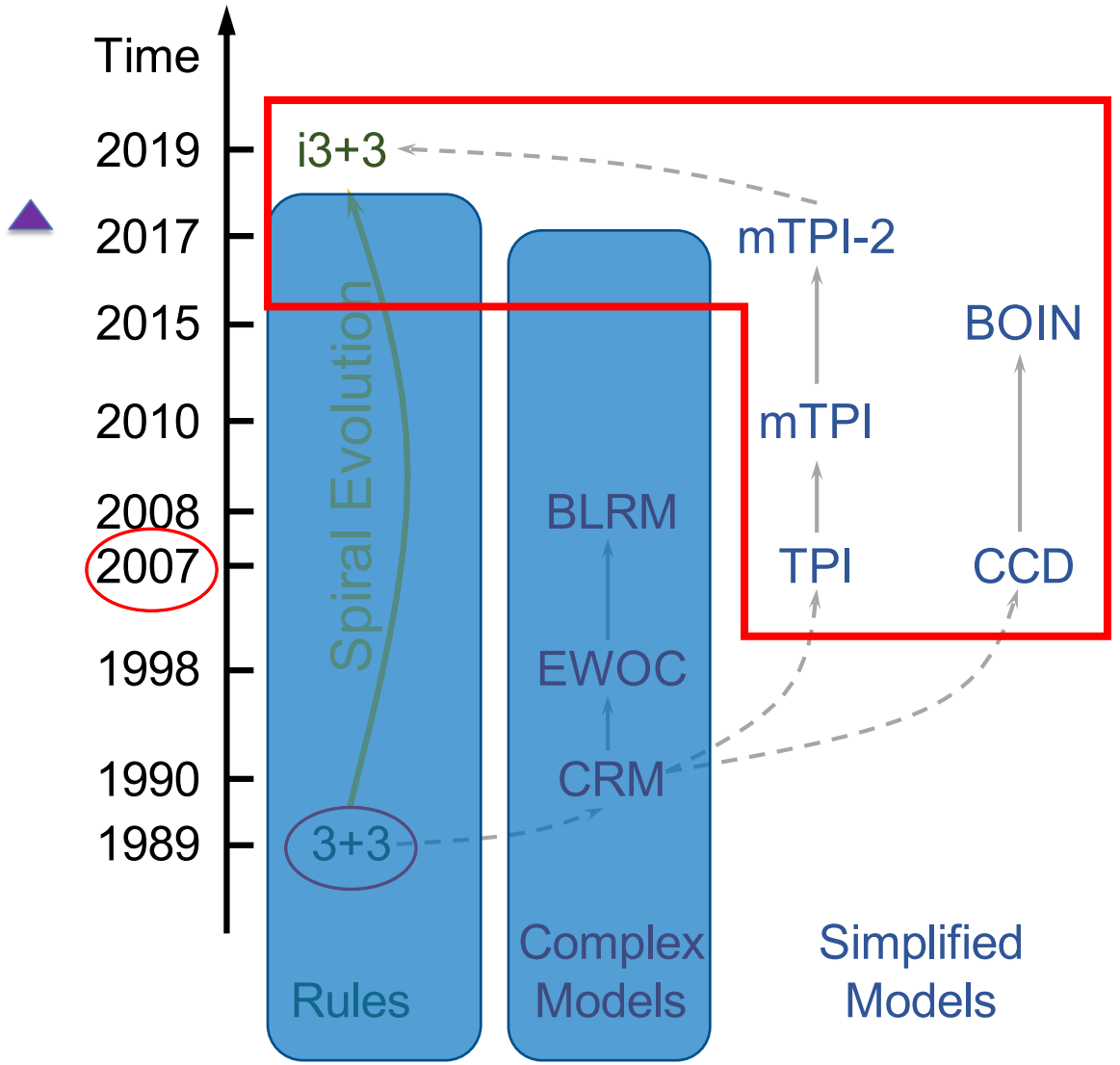
- First paper, O'Quigley, Fisher, Pepe (1990); solid statistical principle: Model-based inference; borrow information across doses
- Wheeler et al. (2019) provide a comprehensive tutorial summarizing the decades of research on CRM.
- CRM is not easy to implement – in 2019 still needing a tutorial

# CRM-Software (Wheeler et al., 2019)

| Name | Host/Institution | Software/Stand-alone | Free/Commercial | Rule-based/Model-based | Description |
|---|---|---|---|---|---|
| bcrm [88] | CRAN | R | Free | Both | Design, run, and simulate trials using the CRM and 3 + 3 design |
| dfcrm [18] | CRAN | R | Free | Model-based | Design, run, and simulate trials using the CRM and Time-to-event CRM |
| crmPack [89] | CRAN | R | Free | Both | Design, run, and simulate trials using the CRM (includes other model-based designs, joint toxicity-efficacy modelling) |
| crm [90] | IDEAS (RePEc) | Stata | Free | Model-based | Run a single trial using the CRM |
| MoDEsT [91] | Lancaster University | Stand-alone (online) | Free | Model-based | Design, run, and simulate trials using the CRM |
| Bayesian CRM for phase I trials [92] | University of Virginia | Stand-alone (online) | Free | Model-based | Design, run, and simulate trials using the CRM |
| AplusB [93] | MRC Biostatistics Unit, University of Cambridge | Stand-alone (online) | Free | Rule-based | Compute exact operating characteristics for 3 + 3 and other rule-based designs |
| Center for Quantitative Sciences Calculator [94] | Vanderbilt University | Stand-alone (online) | Free | Both | Simulate trials using the CRM (uses bcrm [88] and dfcrm [18]) and other designs (rule-based/model-based) |
| CRMSimulator [95] | MD Anderson Cancer Center, University of Texas | Stand-alone | Free | Model-based | Simulate trials using the CRM |
| FACTS [96] | Berry Consultants | Stand-alone | Commercial | Both | Design program for phase I trials using the CRM, plus fixed and adaptive designs for phase II trials |
| ADDPLAN [97] | ICON PLC | Stand-alone | Commercial | Both | Design, simulate, and analyse trials using the CRM (includes methods for dose-response modelling) |
| ~~U-Design~~ | ~~Laiya Consulting~~ | ~~Stand-alone~~ | ~~Commercial~~ | ~~Both~~ | ~~Phase I, II, II/III adaptive designs, master protocols sample size cal; etc.~~ |
| EAST Bayes | Cytel | Stand-alone | Commercial | Both | Phase I adaptive designs, |

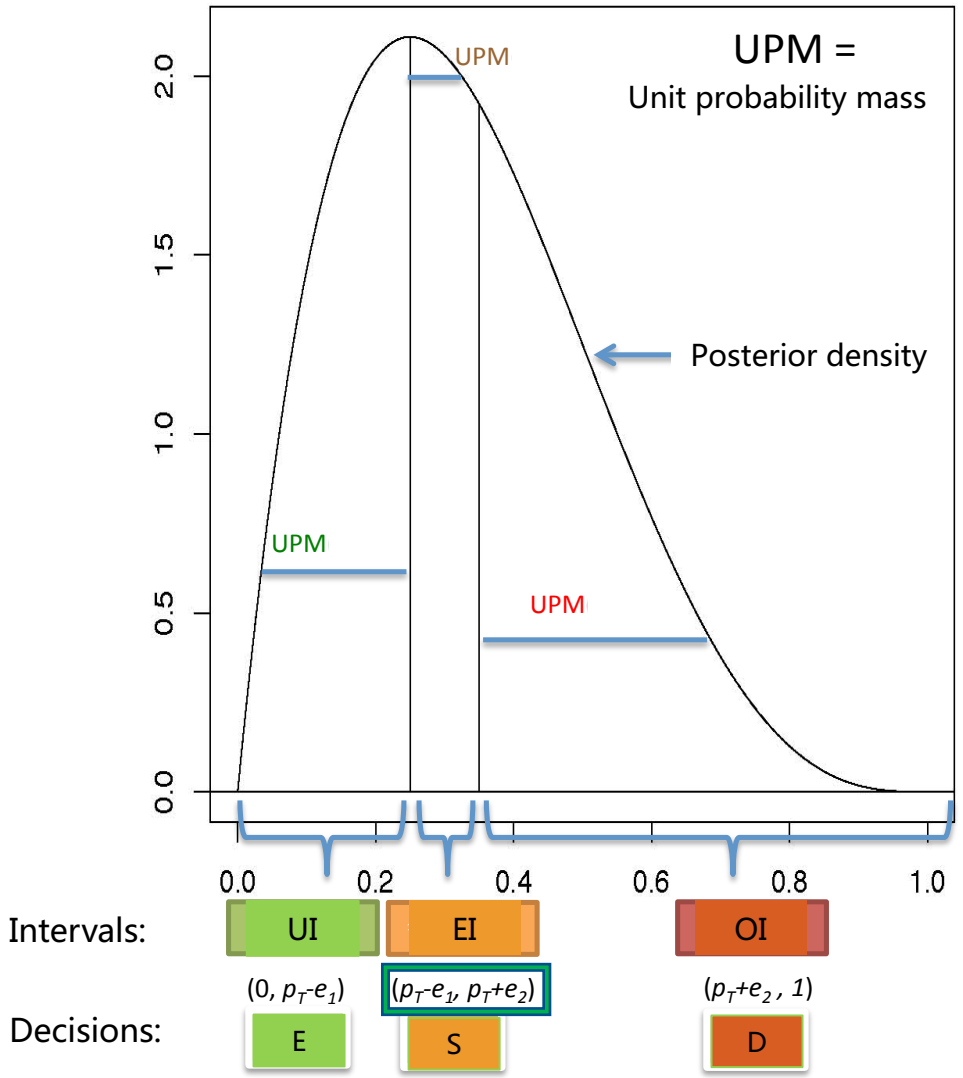
# The interval-based designs (2007-now)

- Model-based designs
  - Account for variability
  - ~~Dose response curves~~
  - Flexible and powerful
- Simple & Transparent
  - ~~Over-dose control~~
  - Simple Bayesian models
  - Decision tables



# The mTPI (mTPI-2) designs: Specify an equivalence interval

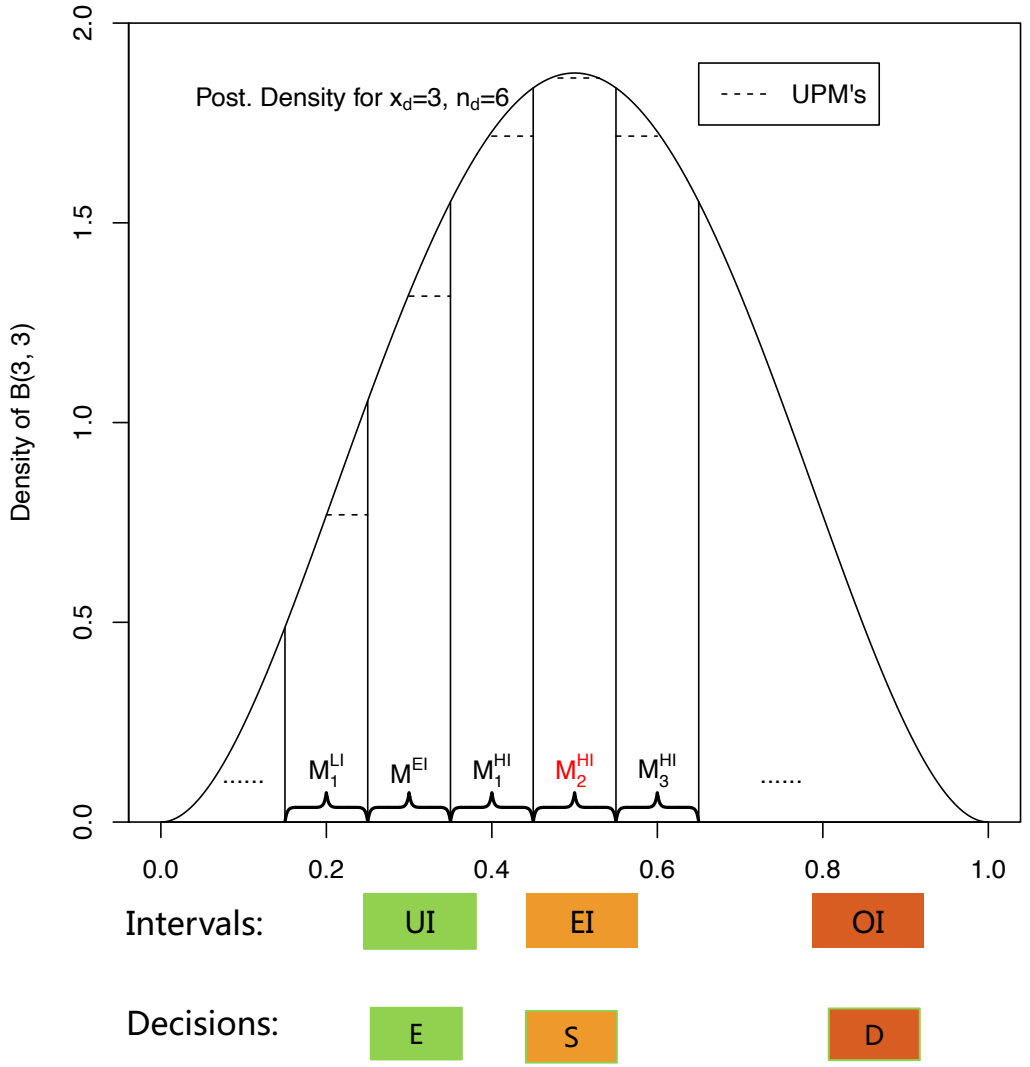
- MTD target is set at $p_T$, say 0.25.
- An equivalence interval $(p_T - \epsilon_1, p_T + \epsilon_2)$, where $(p_T - \epsilon_1)$ and $(p_T + \epsilon_2)$ are the lowest and highest toxicity rates for a dose to be considered as the MTD.
- All the decisions for dose finding can be pre-tabulated (Ji et al., 2007, 2010)




UPM = Marginal posterior probability of interval (Guo et al., 2017)

# The mTPI (mTPI-2) designs: Equal-lengthed subintervals

- MTD target is set at $p_T$, say 0.25.
- Due to Ockham's razor (Guo et al., 2017), mTPI-2 further divides the three intervals into subintervals with equal length.
- mTPI-2 (Guo et al, 2017) and keyboard (Yan et al, 2017) are identical.



Sample size = 9 ; Target toxicity probability = 30% ; epsilon 1 = 0.05 ; epsilon 2 = 0.05 ;

Number of Patients

| Number of DLTs | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|---|
| 0 | E | E | E | E | E | E | E | E | E |
| 1 | D | S | S | S | S | E | E | E | E |
| 2 | | DU | D | S | S | S | S | S | S |
| 3 | | | DU | DU | D | S | S | S | S |
| 4 | | | | DU | DU | DU | D | D | S |
| 5 | | | | | DU | DU | DU | DU | DU |
| 6 | | | | | | DU | DU | DU | DU |
| 7 | | | | | | | DU | DU | DU |
| 8 | | | | | | | | DU | DU |
| 9 | | | | | | | | | DU |

E: Escalate to the next higher dose; S: Stay at the same dose; D: De-escalate to the previous lower dose; DU: De-escalate to the previous lower dose and the current dose will never be used again in the trial;

# An mTPI decision table

- Generated based on models
- Presented as rules

# Contribution to the society: Interval-based designs (2007-2013) & (2015-2020)

= 9 ; Target toxicity probability = 30% ; epsilon 1 = 0.05 ; epsilon 2 = 0.05 ;

**Number of Patients**

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | |
|---|---|---|---|---|---|---|---|---|
| E | E | E | E | E | E | E | E | |
| D | S | S | S | S | E | E | E | |
| | DU | D | S | S | S | S | S | |
| | | DU | DU | D | S | S | S | |
| | | | DU | DU | DU | D | D | |
| | | | | DU | DU | DU | DU | |
| | | | | | DU | DU | DU | |
| | | | | | | DU | DU | |
| | | | | | | | DU | |
| | | | | | | | | |

to the next higher dose; **S**: Stay at the same dose; **D**: De-escalate to the previous lower dose; **DU**: De-escalate to the and the current dose will never be used again in the trial;

- For the first time bridged simple rules with model-based inference
- Effectively challenged the 3+3 design as the only clinically popular method
- Widely used in practical trials (publications in Lancet Oncology, JAMA Oncology, etc)
- CCD/BOIN/i3+3 further simplify the interval ideas

Number of Patients

| Number of DLTs | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|---|
| 0 | E | E | E | E | E | E | E | E | E |
| 1 | D | S | S | S | S | E | E | E | E |
| 2 | | DU | D | S | S | S | S | S | S |
| 3 | | | DU | DU | D | S | S | S | S |
| 4 | | | | DU | DU | DU | D | D | S |
| 5 | | | | | DU | DU | DU | DU | DU |
| 6 | | | | | | DU | DU | DU | DU |
| 7 | | | | | | | DU | DU | DU |
| 8 | | | | | | | | DU | DU |

# A criticism of the mTPI design table

When 3/6 patients have DLT, how can we "S", stay at the current dose?

---

Note: 2/4 – S; but 4/8 – D!

# The mTPI decisions are statistically optimal, but

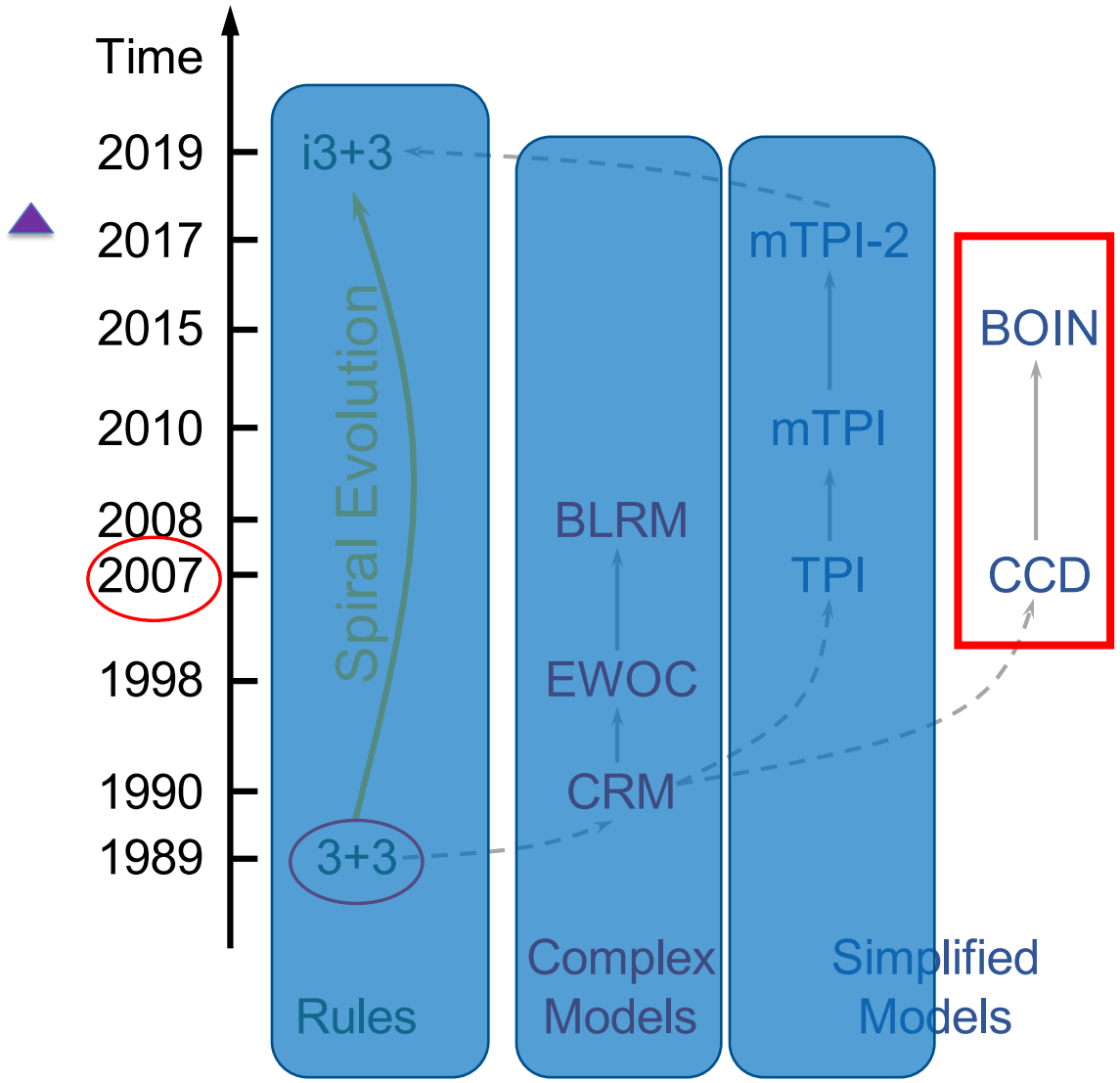
- Guo et al. (2017) show that the decisions in mTPI minimizes the posterior expected 0-1 loss – it is statistically optimal!
- So how can Stay at 3/6 be an optimal decision?
  - 3/6 Stay when $p_T = 0.3$ and EI=(0.25, 0.35). Is it wrong?
  - 4/8 De-escalate based on the same table
  - Statistical variability is the key; 6 patients have larger variability than 8 patients;
  - Alternatives:
    - Change 0-1 loss to a loss based on distance from $p_T$
    - Ockham's razor: Guo et al. (2017) – the mTPI-2 design
    - mTPI-2 blunts Ockham's razor and makes decisions more "nimble"

**Number of Patients**

| Number of DLTs | 1 | | 2 | | 3 | | 4 | | 5 | | 6 | | 7 | | 8 | | 9 | | 10 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | mTPI | mTPI2 | mTPI | mTPI2 | mTPI | mTPI2 | mTPI | mTPI2 | mTPI | mTPI2 | mTPI | mTPI2 | mTPI | mTPI2 | mTPI | mTPI2 | mTPI | mTPI2 | mTPI | mTPI2 |
| 0 | E | E | E | E | E | E | E | E | E | E | E | E | E | E | E | E | E | E | E | E |
| 1 | D | D | S | D | S | S | S | S | S | E | E | E | E | E | E | E | E | E | E | E |
| 2 | | | DU | DU | D | D | S | D | S | D | S | S | S | S | S | S | S | E | S | E |
| 3 | | | | | DU | DU | DU | DU | D | D | S | D | S | D | S | D | S | S | S | S |
| 4 | | | | | | | DU | DU | DU | DU | DU | DU | D | D | D | D | S | D | S | D |
| 5 | | | | | | | | | DU | DU | DU | DU | DU | DU | DU | DU | DU | DU | D | D |
| 6 | | | | | | | | | | | DU | DU | DU | DU | DU | DU | DU | DU | DU | DU |
| 7 | | | | | | | | | | | | | DU | DU | DU | DU | DU | DU | DU | DU |
| 8 | | | | | | | | | | | | | | | DU | DU | DU | DU | DU | DU |
| 9 | | | | | | | | | | | | | | | | | DU | DU | DU | DU |

# The interval designs (2015-now)

- Model-assisted designs
  - Statistical inference using models (simple models)
  - Inference based on point estimate
  - Presentation of the decisions as rules



# What is the BOIN design and why is it popular?

- At a dose, **n** (e.g., =3, 6, 9) patients are treated, **y** (=0, 1, 2,⋯) patients DLT
- Compare $\frac{y}{n}$ with intervals
  - If $\frac{y}{n} \leq p_T - e_1^*$, Escalate
  - If $p_T - e_1^* < \frac{y}{n} < p_T + e_2^*$, Stay
  - If $\frac{y}{n} \geq p_T + e_2^*$, De-escalate
- The above rules **originally proposed by the CCD design** (Ivanova et al., 2007)
- BOIN applies the same safety rules as in mTPI

Examples: $p_T$ = 0.3, interval = (0.25, 0.35)

0/3, Escalate; 1/3 Stay, 2/3, 3/3 De-escalate

0/6, 1/6, Escalate; 2/6 Stay, 3/6, 4/6, 5/6, 6/6 De-escalate

BOIN is very simple and easy to use. However,
What are the $e_1^*$ and $e_2^*$ and how to decide them?

Quick answer: elicit from physicians.

BOIN: "O" stands for "optimal", but

$e_1^*$ and $e_2^*$ are based on an optimization procedure.

- Physicians provide an interval
  $(p_T - \epsilon_1, p_T + \epsilon_2)$
- BOIN changes it to "**optimal**"
  $(p_T - e_1^*, p_T + e_2^*)$

# How does the optimization work in BOIN? (Duan et al., 2022)

## A decision framework requires a reasonable model

Data: $y$; Model: f$(y|\theta)$, Prior: $\pi(\theta)$, Posterior: $p(\theta|y)$

Action: $a \in \{D, S, E\}$; Loss: $l(a,\theta)$, Decision rule: $R(y) \to a$

Optional decision rule: $R^*(y)$ is optimal if it provides the smallest loss (or expected loss); for example, Bayes' rule

$R^*(y) = \arg\max_a \int l(a,\theta)p(\theta|y)d\theta$

mTPI/mTPI-2/keyboard are based on Bayes' rules for a model

f$(y|\theta) = Bin(n,\theta)$, $\pi(\theta|interval) = beta(1,1)Ind(interval), \pi(interval) = unf$

and 0-1 loss

## BOIN decisions correspond to a Bayes rule with a prior distribution assumes three point masses

Model: f$(y|\theta) = Bin(n,\theta)$; Prior: $\pi(\theta) = \frac{1}{3}$ if $\theta \in \{p_T - e_1^*, p_T, p_T + e_2^*\}$

Loss: 0-1 loss $Ind(a = D, \theta \neq \phi_2) + Ind(a = S, \theta \neq p_T) + Ind(a = E, \theta \neq \phi_1)$

Optimal decision: Bayes' rule

if $\frac{y}{n} \leq p_T - e_1^*$, E(scalate)

if $p_T - e_1^* < \frac{y}{n} < p_T + e_2^*$, S(tay)

if $\frac{y}{n} > p_T + e_2^*$, D(e-escalate)

Note: The $e_1^*$ *and* $e_2^*$ can be derived based on optimization using Bayes' rule.

# FDA fit-for-purpose designation for BOIN

- FFP-BOIN: FDA FFP-designated BOIN; O-BOIN: the original BOIN design in Liu and Ying (2015)

- The FFP-BOIN design is different from the originally published O-BOIN design. The following table provides a comparison between the two designs.

- In addition, the FFP-BOIN design only uses the "non-informative prior" where the prior probabilities of the three point hypotheses in O-BOIN are equal, i.e., $\pi_{0j} = \pi_{1j} = \pi_{2j} = 1/3$. The O-BOIN design is not restricted to this prior. The FDA review also pointed some issues with using priors outside the conditions on $\pi$'s. See https://www.fda.gov/media/155364/download for more details.

| | O-BOIN | FFP-BOIN |
|---|---|---|
| **Bounds of $\lambda_{1j}$ and $\lambda_{2j}$** | $0 \leq \lambda_{1j}(n_j, \phi) < \lambda_{2j}(n_j, \phi) \leq 1$ | $\lambda_{1j}(n_j, \phi) \leq \lambda_{2j}(n_j, \phi)$ |
| **De-escalate Decision** | if $\hat{p}_j \geq \lambda_{2j}(n_j, \phi)$ | if $\hat{p}_j > \lambda_{2j}(n_j, \phi)$ |
| **Retain Decision** | if $\lambda_{1j}(n_j, \phi) < \hat{p}_j < \lambda_{2j}(n_j, \phi)$ | if $\lambda_{1j}(n_j, \phi) < \hat{p}_j \leq \lambda_{2j}(n_j, \phi)$ |

# One may not need simulations to evaluate interval-based designs!

**Number of Patients**

| | 2 | | 3 | | 4 | | 5 | | 6 | | 7 | | 8 | | 9 | | 10 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | mTPI | mTPI2 | mTPI | mTPI2 | mTPI | mTPI2 | mTPI | mTPI2 | mTPI | mTPI2 | mTPI | mTPI2 | mTPI | mTPI2 | mTPI | mTPI2 | mTPI | mTPI2 |
| | E | E | E | E | E | E | E | E | E | E | E | E | E | E | E | E | E | E |
| | S | D | S | S | S | S | S | E | E | E | E | E | E | E | E | E | E | E |
| | DU | DU | D | D | S | D | S | D | S | S | S | S | S | S | S | E | S | E |
| | | | DU | DU | DU | DU | D | D | S | D | S | D | S | D | S | S | S | S |
| | | | | | DU | DU | DU | DU | DU | DU | D | D | D | D | S | D | S | D |
| | | | | | | | DU | DU | DU | DU | DU | DU | DU | DU | DU | DU | D | D |
| | | | | | | | | | DU | DU | DU | DU | DU | DU | DU | DU | DU | DU |
| | | | | | | | | | | | DU | DU | DU | DU | DU | DU | DU | DU |
| | | | | | | | | | | | | | DU | DU | DU | DU | DU | DU |
| | | | | | | | | | | | | | | | DU | DU | DU | DU |
| | | | | | | | | | | | | | | | | | DU | DU |

e next higher dose; **S**: Stay at the same dose; **D**: De-escalate to the previous lower dose; **DU**: De-escalate to the se and the current dose will never be used again in the trial;

- Interval-based designs contain three key components:
  - i. Safety rules that stop trials or exclude doses if $\Pr(p_d \text{ or } p_1 > p_T | data) > 0.95$
  - ii. MTD selection procedure: for example, $\text{argmin}|\hat{p}(x) - p_T|$ where $\hat{p}(x)$ is isotonic transformed posterior mean
  - iii. The pretabulated decision tables

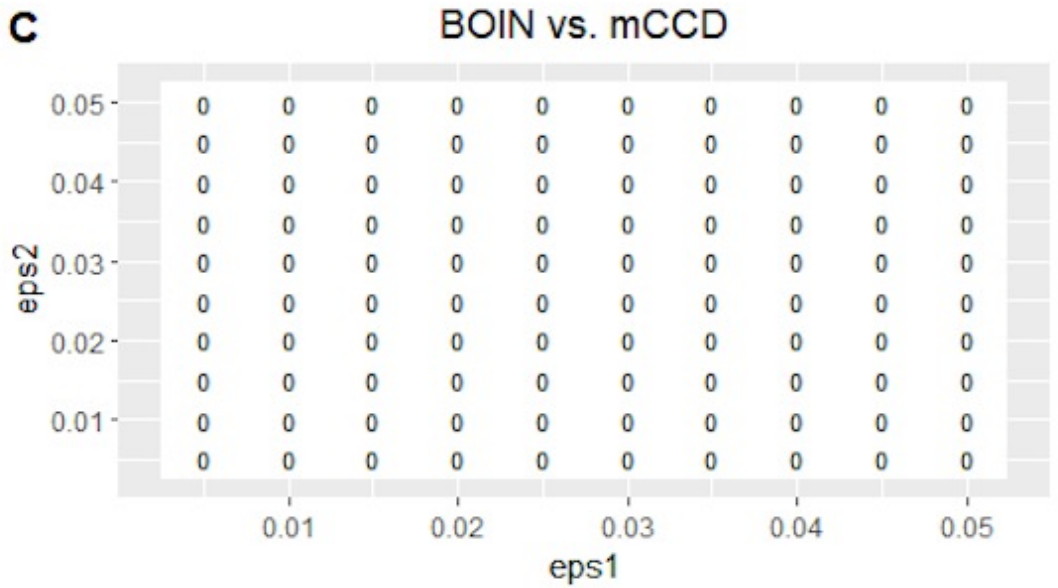
The mTPI, mTPI-2/keyboard, BOIN, i3+3 have identical i and ii. The only differences are in iii.

# Without running simulations one can already evaluate interval-based designs – BOIN and CCD

- BOIN and mCCD (mCCD = CCD + safety rules)

  have the same i & ii; and for iii mCCD does not optimize the EI

- The decisions b/w BOIN and mCCD are identical (for <=51 ss)




Differences = 0 out of a total 1,326 decisions ; $p_T = 0.3$

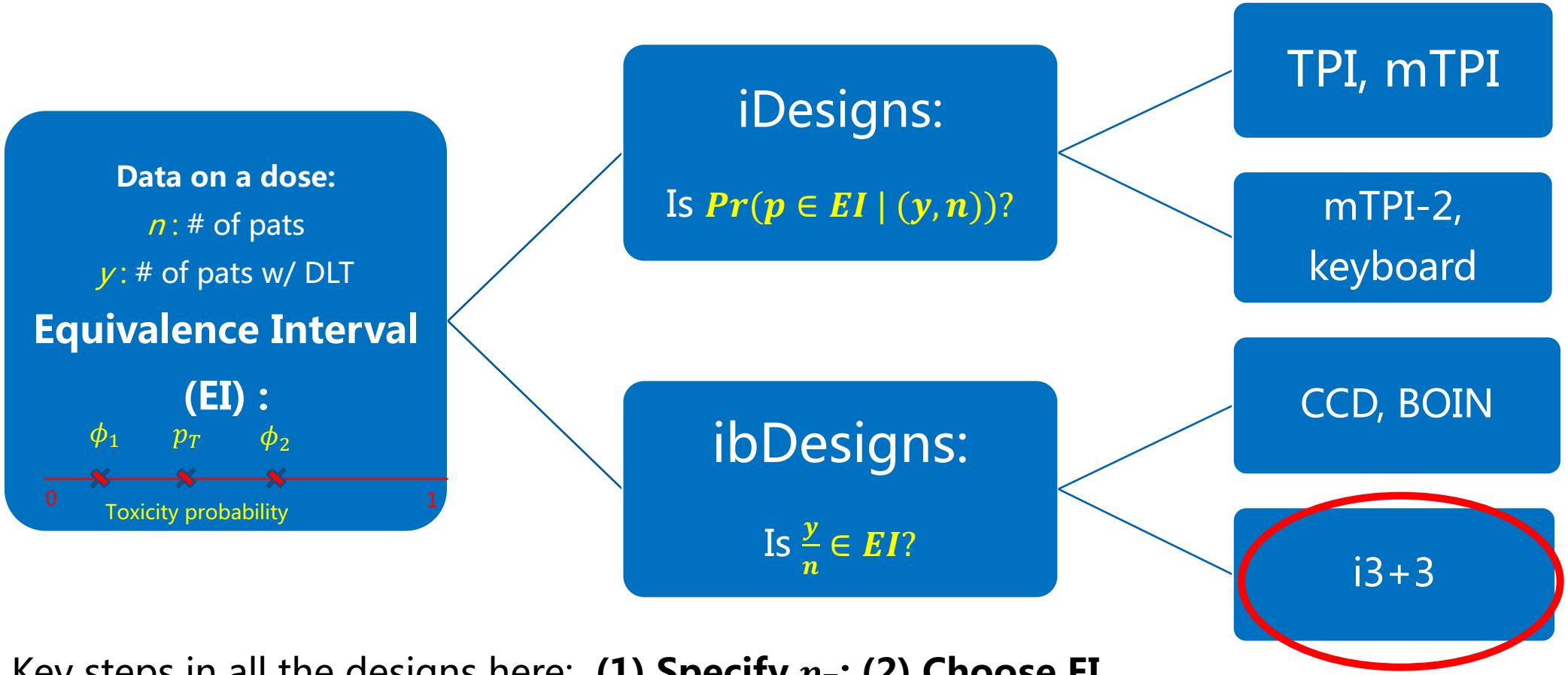
# Simulation results can be misleading

- For interval-based designs; just look for the three components:
  i. Safety rules
  ii. MTD selection
  iii. Decision tables

- Simulation results for interval designs based on repeated computer-generated clinical trials are completed decided by i - iii.

- Read review papers with caution
  - No single design can dominate another design in ALL scenarios

# The interval designs (iDesigns) and the interval-boundary designs (ibDesigns)

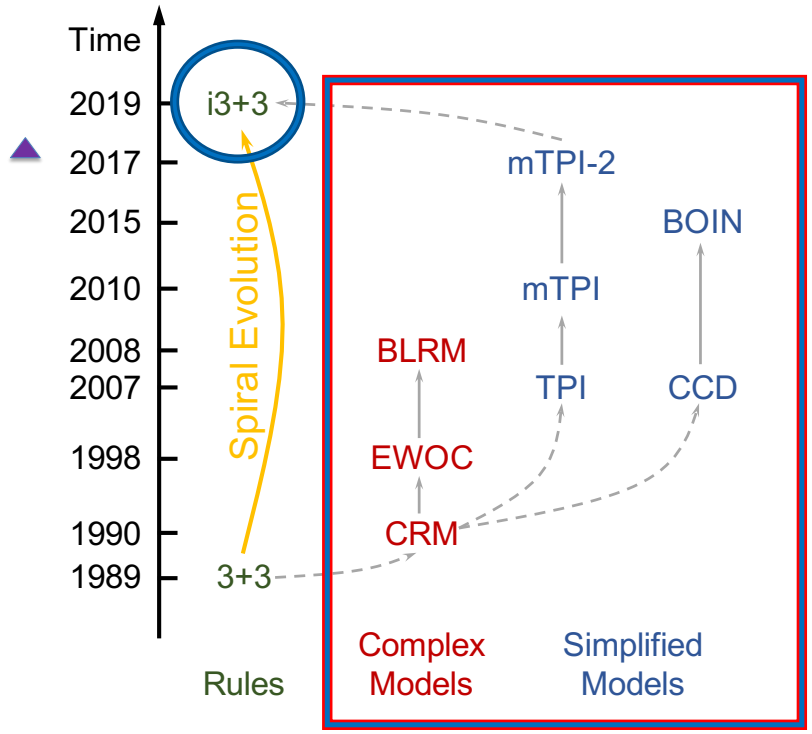



- Key steps in all the designs here: **(1) Specify $p_T$; (2) Choose EI**
- All the designs here use **the same isotonic regression** to choose final MTD
- Except CCD, all the designs have **the same safety rules**

# Statistical modeling is about variabilities: 3/6=0.5; 30/60=0.5, 3000/6000=0.5…

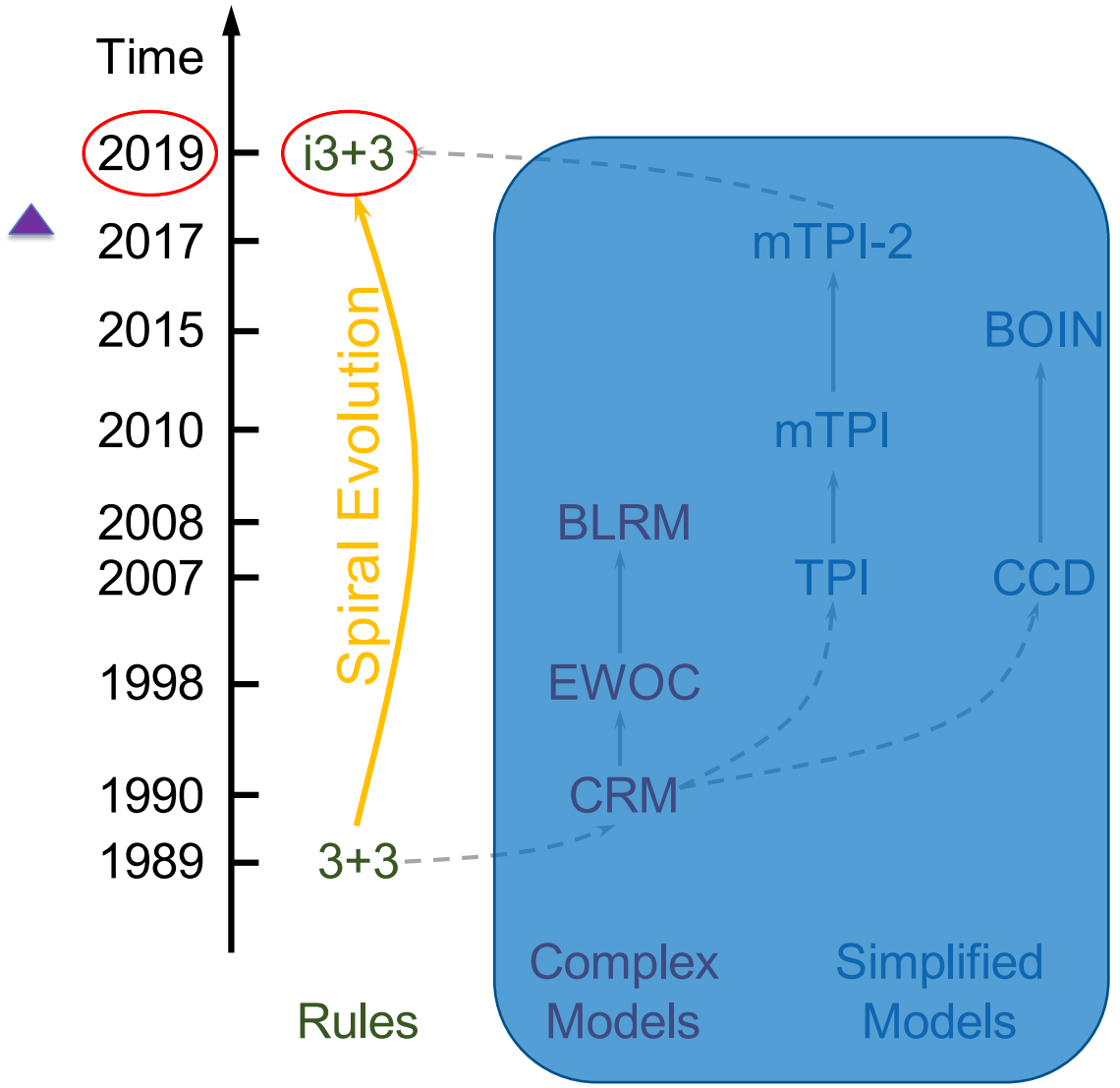
- The hallmark of statistics is variability
  - If no variability, no need for statistics!
  - But the rules below ignore variability!
    - If $\frac{y}{n} \leq p_T - \lambda_1$, Escalate;
    - If $p_T - \lambda_1 < \frac{y}{n} < p_T + \lambda_2$, Stay;
    - If $\frac{y}{n} \geq p_T + \lambda_2$, De-escalate
- Remember this picture?
  - We spent 30 years resorting to statistical models
  - Because models account for variability
  - But if in the end the decision rules do not need to account for variability; why bothering with models?

The last chapter: back to rule-based designs!



# The i3+3 design (2019)

- Rule based (smart rules)
- No statistical model
  - Easy
  - Transparent
  - Social acceptance
- Flexible and powerful



# The i3+3 design (Liu, Wang, Ji, 2020, JBS)

- If $\frac{y}{n} < p_T - e_1$, ⟶ Escalate;
- If $p_T - e_1 \le \frac{y}{n} \le p_T + e_2$, ⟶ Stay;
- If $\frac{y}{n} > p_T + e_2$,
  1. If $\frac{y-1}{n} < p_T - e_1$, ⟶ Stay;
  2. Else, ⟶ De-escalate;

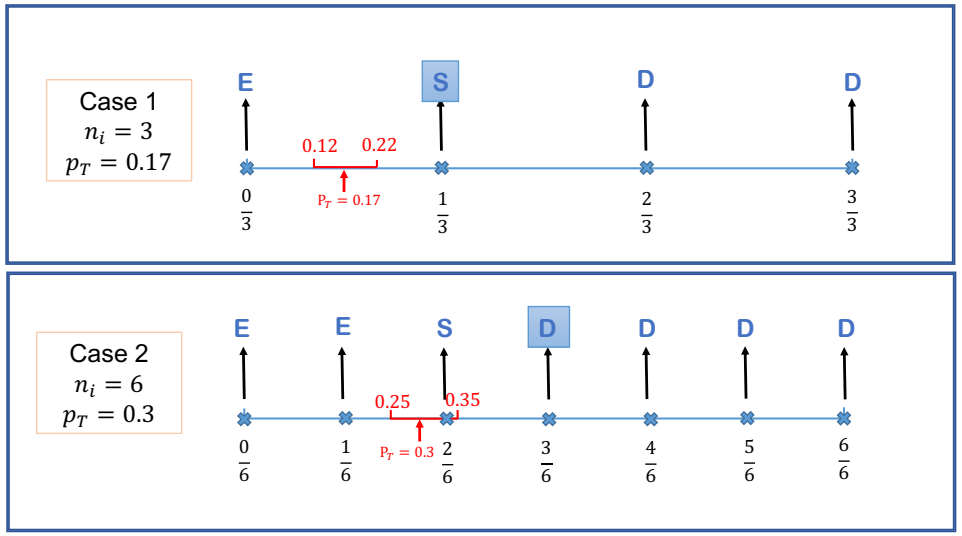
Examples: $p_T$ = 0.3, EI = (0.25, 0.33)

| *i3+3:* | *mTPI-2/BOIN:* |
|---|---|
| 0/3 – Escalate; | 0/3 – Escalate; |
| 1/3 – Stay; | 1/3 – De-escalate; |
| 2,3/3 – De-escalate | 2,3/3 – De-escalate |

When $\frac{1}{n} < e_1 + e_2$, i3+3, CCD, and BOIN have identical decisions as long as they use the same EI

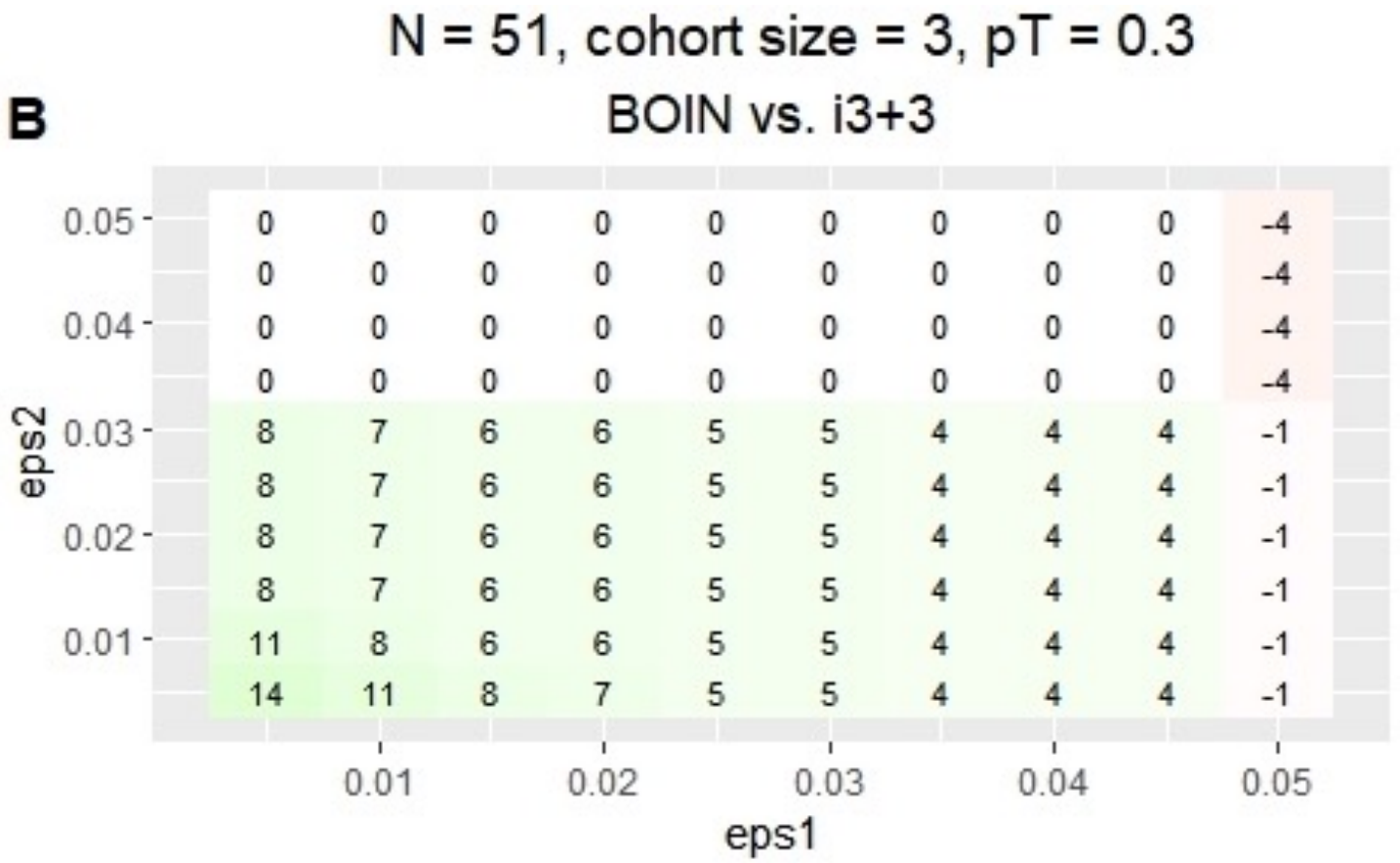
# The i3+3 decision rules (two examples)

- Comparison to mTPI and BOIN when 1/n is large




| **Current dose:** $d$<br>**No. enrolled:** $n = 6$ | **Target probability:** $p_T = 0.3$<br>**EI:** $[p_T - \epsilon_1, p_T + \epsilon_2] = [0.25, 0.35]$ | | |
|---|---|---|---|
| **No. DLTs:** $x$ | Next dose level | | |
| | i3+3 | mTPI | BOIN |
| 0 | $d+1$ | $d+1$ | $d+1$ |
| 1 | $d+1$ | $d+1$ | $d+1$ |
| 2 | $d$ | $d$ | $d$ |
| 3 | $d-1$ | $d$ | $d-1$ |
| 4 | $d-1$ | $d-1$ | $d-1$ |
| 5 | $d-1$ | $d-1$ | $d-1$ |
| 6 | $d-1$ | $d-1$ | $d-1$ |

| **Current dose:** $d$<br>**No. enrolled:** $n = 3$ | **Target probability:** $p_T = 0.17$<br>**EI:** $[p_T - \epsilon_1, p_T + \epsilon_2] = [0.12, 0.22]$ | | |
|---|---|---|---|
| **No. DLTs:** $x$ | Next dose level | | |
| | i3+3 | mTPI | BOIN |
| 0 | $d+1$ | $d+1$ | $d+1$ |
| 1 | $d$ | $d$ | $d-1$ |
| 2 | $d-1$ | $d-1$ | $d-1$ |
| 3 | $d-1$ | $d-1$ | $d-1$ |




Differences in about 1% out of a total 1,326 decisions

# So how does i3+3 perform?

- For interval-based designs; just look for the three components:
  - Safety rules
  - MTD selection
  - Decision tables
- With only tiny differences the two designs perform comparably

# How to evaluate the simulation results? Lots of summary statistics; can be difficult to compare

## Scenario 1

Simulated Dose Escalation

| $p_T$ = 0.25, $n_{sim}$ = 1000 | | Selection Prob. | | Average # of Patients Treated (s.d.) | | Average # of Toxicities (s.d.) | |
|---|---|---|---|---|---|---|---|
| Dose Level | True Tox Prob. | mTPI-2 | mCCD | mTPI-2 | mCCD | mTPI-2 | mCCD |
| 1 | 0.13 | 0.375 | 0.234 | 12.072 (8.092) | 11.781 (7.821) | 1.605 (1.961) | 1.575 (1.929) |
| 2 | 0.25 | 0.491 | 0.555 | 11.646 (5.862) | 11.634 (5.625) | 2.88 (1.912) | 2.842 (1.9) |
| 3 | 0.38 | 0.112 | 0.191 | 5.016 (5.313) | 5.28 (5.231) | 1.908 (1.987) | 2.025 (1.985) |
| 4 | 0.5 | 0.008 | 0.012 | 1.038 (2.449) | 1.077 (2.481) | 0.528 (1.228) | 0.549 (1.245) |
| 5 | 0.63 | 0 | 0.001 | 0.102 (0.649) | 0.102 (0.649) | 0.075 (0.479) | 0.075 (0.479) |

| | | mTPI-2 | mCCD |
|---|---|---|---|
| MTD Selection | Prob. of Selecting MTD | 0.491 | 0.555 |
| | Prob. of Selecting Dose-over-MTD | 0.12 | 0.204 |
| | Prob. of No Selection | 0.014 | 0.007 |
| Patients Assignment | Prob. of Correct Allocation (s.d.) | 0.388 (0.195) | 0.388 (0.187) |
| | Prob. of Overdosing Allocation (s.d.) | 0.205 (0.234) | 0.215 (0.231) |
| Trial Toxicity | Prob. of Toxicity | 0.234 | 0.237 |
| Trial Stopping** | Prob. of Early Stopping Trial due to Safety Rule | 0.007 | 0.007 |
| | Prob. of Early Stopping Trial due to Reaching $K$ | 0 | 0 |
| | Prob. of Stopping Trial due to Reaching $n$ | 0.993 | 0.993 |
| Trial Sample Size | Average # of Patients Treated (s.d.) | 29.874 (1.622) | 29.874 (1.622) |

Less

* The row with background color indicates the TRUE MTD

** For further details concerning Trial Stopping Rule, please refer to section 1.2.2 in the User Manual.

# The J-Score is a weighted average of MTD selection and patient allocation

$$Utility_{iA} = R_1 \times \%SelAtMTD_i - p_{l_1} \times \%SelBelowMTD_i - p_{h_1} \times \%SelAboveMTD_i$$

and

$$Utility_{iB} = R_2 \times \%PntAtMTD_i - p_{l_2} \times \%PntBelowMTD_i - p_{h_2} \times \%PntAboveMTD_i$$

The total utility for design $i$ is defined as the sum of the two utilities:

$$Utility_i = Utility_{iA} + Utility_{iB}$$

and for $i = 1, ..., I$ designs, $\mathbf{Utility} = \{Utility_i\}$ denotes the vector of the designs that are under comparison.

The J-score, which is the continuous rank index of the total utility, is thus defined as:

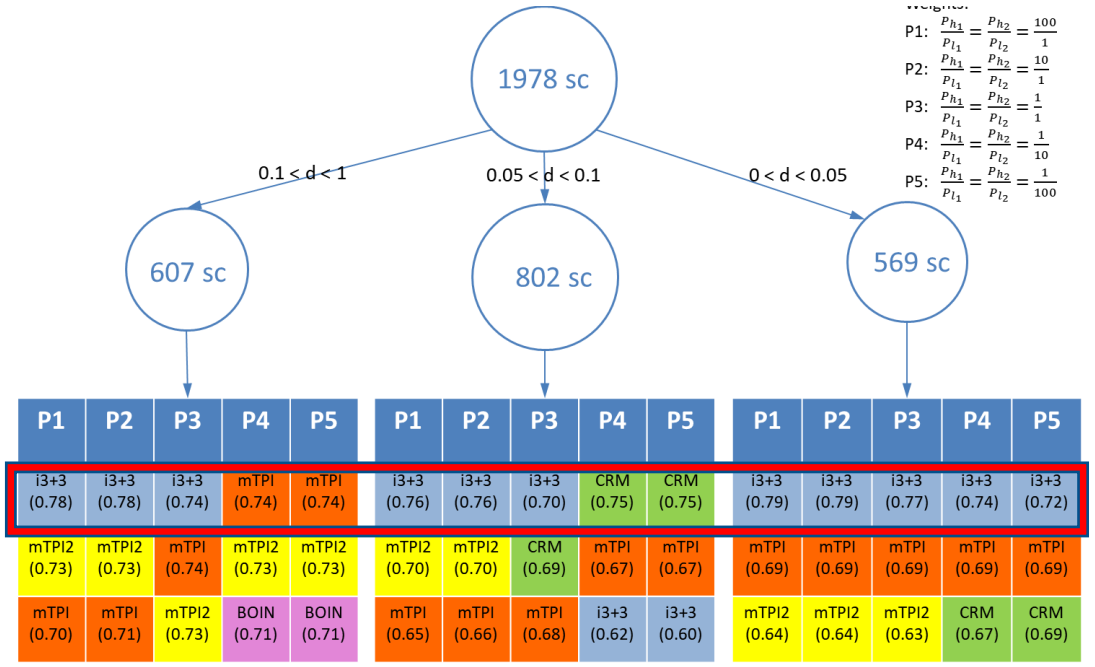
$$Jscore_i = \frac{Utility_i - \min(\mathbf{Utility})}{\max(\mathbf{Utility}) - \min(\mathbf{Utility})}$$

J score is between 0 and 1; the larger value, the better the design

# J-Score results: Different designs perform better in different types of scenarios

- Based on 1,978 scenarios from users
- Massive simulations
- A tree summarizes the best designs based on scenarios and drug development preferences
  - Aggressive: P1, P2
  - Neutral: P3
  - Conservative: P4, P5
- A higher score means better
  - High probability of selecting the MTD
  - Safe in allocating patients
  - Safe in selecting the doses

d – distance between MTD and adjacent doses; larger value means easier scenario




Top performers for each category

# My Personal and Personalized Recommendation

For non-statisticians and performance-driven practioners who are less concerned about statistical theory:

i3+3,

BOIN,

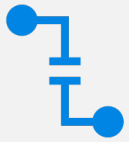
CCD (with modification)

For statisticians who balance between principled inference and practical considerations:

mTPI , mTPI-2,

keyboard,

SPM



For statisticians who mostly focus on principled and model-based inference:

CRM,

BLRM,

EWOC

# Summary

1. Model-based methods are more powerful
   - Yes, but depends on what you care (simplicity; model-misspecification; 1/3 Stay no matter what)

2. mTPI is not safe
   - Yes, but depends on your loss function (e.g., 3/6 is not too much, but 4/8 is)

3. CCD and BOIN are model-assisted designs
   - Yes, model-assisted is still model-based

4. mTPI, mTPI-2, BOIN, Keyboard
   - They are model-based designs; and mTPI-2 = Keyboard

5. Which designs to use? Depends!
   - For classical single-agent DLT-based cohort—enrollment phase 1 trial, physicians can use i3+3 or mTPI-2, but mostly i3+3, unless your drug is very very safe (future talk)
   - CRM is also really good but requires statistical expertise and support
   - BOIN performs really well and is simple; but it has theoretical flaws
   - It seems that

heavy safety regulation + simple model/inference ≈ Model-free (rule-based) design

# Phase I Trials in oncology is becoming more sophisticated and powerful

- Seamless Phase 1a dose finding + Phase 1b cohort expansion
  - Bayesian hierarchical models for borrowing information
- Immune and targeted therapies
  - MTD may not be the RP2D;
  - Multiple candidate doses for expansion
  - Multiple indications (NSCLC, GC, Ovarian, Prostate, RCC, etc)
- Delayed toxicity outcomes
- Combination treatments (novel + novel combo)
- Eff/Tox dose finding (for cell/gene therapies, e.g., CAR-T)
- Rolling enrollment to speed up the trial
- Borrowing historical data for dose finding (Hi3+3; https://arxiv.org/abs/2010.10244)

# Sotorasib (Lumakras) for NSCLC

Approved in May 2021 for patients with NSCLCs harboring KRAS p.G12C mutation (based on a phase 2 trial)

The first drug successfully targets KRAS, a historically "undruggable" and yet important cancer biomarker

However, a post-marketing trial is required by FDA to further explore lower doses than the approved one

This is due to lack of sufficient dose exploration in early-phase development (e.g., phase 1 with small sample size; dose selection under MTD-regime)

# Oncology drugs with post-market dose modification

**Examples of Drugs Whose Doses or Schedules Were Modified for Safety or Tolerability after Approval.***

| Drug | Initial Dose and Trials | Modified or Added Dose and Trials | Reason for Modified or Added Dose |
|---|---|---|---|
| **Small-molecule drugs** | | | |
| Ceritinib (Zykadia) | 750 mg PO daily fasted (ASCEND-1) | 450 mg PO daily with food (ASCEND-8) | Reduce gastrointestinal toxic effects |
| Dasatinib (Sprycel) | 70 mg PO twice daily (CA180013, CA180005, CA180006, and CA180015) | 100 mg PO daily (CA180034) | Reduce hematologic toxic effects and fluid retention |
| Niraparib (Zejula) | 300 mg PO daily (NOVA) | 200 mg PO daily (PRIMA) | Reduce thrombocytopenia in patients with a lower platelet count or lower body weight |
| Ponatinib (Iclusig) | 45 mg PO daily (PACE) | 45 mg PO daily, then 15 mg PO daily once ≤1% *BCR-ABL* is achieved (OPTIC) | Reduce vascular occlusive events |
| **Chemotherapy** | | | |
| Cabazitaxel (Jevtana) | 25 mg/m$^2$ IV every 3 wk (TROPIC) | 20 mg/m$^2$ IV every 3 wk (PROSELICA) | Reduce hematologic toxic effects and infections |
| **Antibody–drug conjugates** | | | |
| Gemtuzumab ozogamicin (Mylotarg) | 9 mg/m$^2$ IV on days 1 and 15 (Study 201, Study 202, and Study 203) | 3 mg/m$^2$ IV on days 1, 4, and 7 (Mylofrance-1) | Reduce veno-occlusive disease and treatment-related mortality |

* Adapted from the Food and Drug Administration.[2] IV denotes intravenous, and PO by mouth.

Shah et al., 2021, NEJM

- All the listed drugs had to **reduce** their dose or schedule **due to toxicity**

# New Era of Dose Optimization

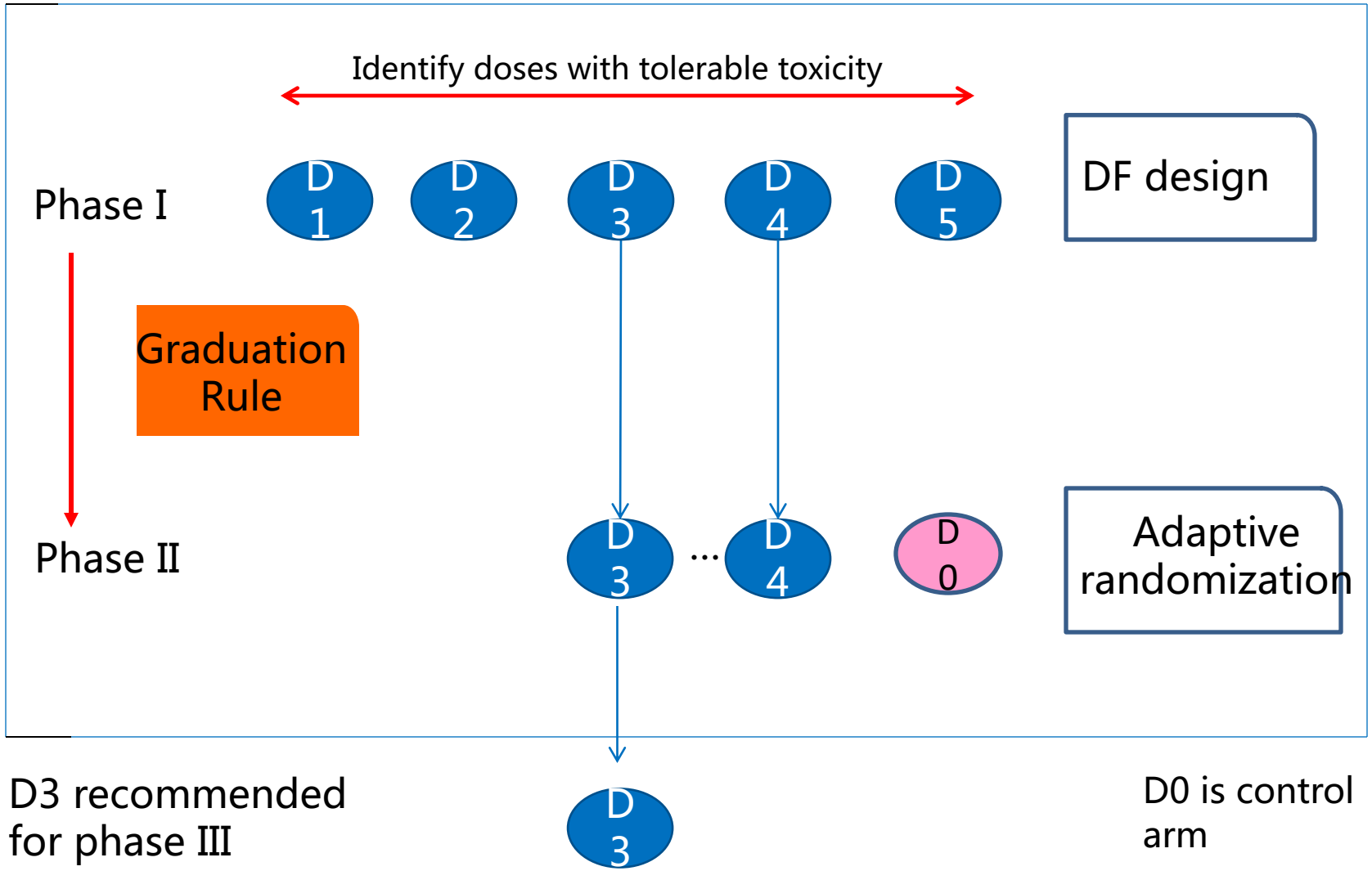
| Higher doses might not have better therapeutic activity | DLT may not be observed at clinically active doses | Serious toxic effects may occur after several cycles of drug usage |
|---|---|---|
| • MTD is no longer the optimal dose | • Dose escalation and dose selection challenges | • Delayed toxicity/efficacy |

# New Era of Dose Optimization: Solutions

| MTD not optimal | DLT may not be observed at clinically active doses | Delayed toxicity/efficacy |
| --- | --- | --- |
| • Eff/Tox dose finding (or Biomarker/Tox) | • Eff/Tox/Exposure dose finding | • Time-to-event (TITE) or Probability of decision (PoD) modeling |

# The SEARS Design (Pan et al., 2014, Clinical Trials)

Seamless phase 1/2 oncology dose optimization trials



# Hi3+3 for borrowing external trial data (https://hi3design.shinyapps.io/hi33_r_shiny/)

**Target toxicity probability $p_T$ :**

0.3

**Equivalence Interval:**

0 0.25 0.35 1

0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1

**Number of doses:**

5

**Max number of patients at one dose**

12

**Max probability of making more aggressive desicions:**

0.1

**Historical data**

| | dose1 | dose2 | dose3 | dose4 | dose5 |
|---|---|---|---|---|---|
| DLTs | 0 | 0 | 1 | 0 | 0 |
| Patients | 1 | 3 | 3 | 0 | 0 |

**Generate Decision Table**

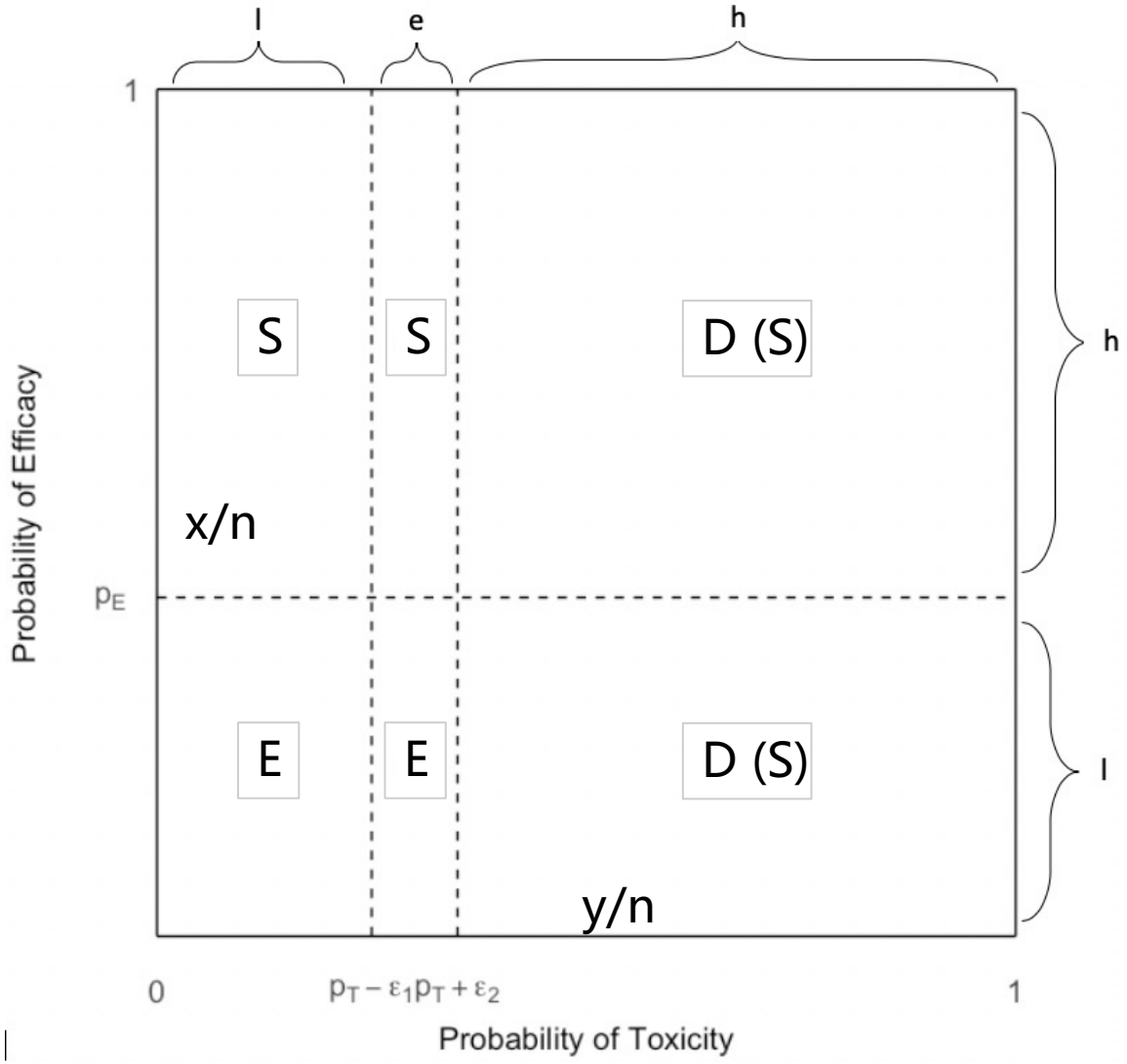
| | omega |
|---|---|
| dose1 | 1.02 |

dose1 dose2 dose3 dose4 dose5

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 0 | E | E | E | E | E | E | E | E | E | E | E | E |
| 1 | S | S | S | E | E | E | E | E | E | E | E | E |
| 2 | D | D | S | S | S | S | E | E | E | E | E | E |
| 3 | DU | D | D | D | D | S | S | S | S | E | | |
| 4 | DU | DU | D | D | D | D | D | S | S | | | |
| 5 | DU | DU | DU | DU | D | D | D | D | | | | |
| 6 | DU | DU | DU | DU | DU | D | D | | | | | |
| 7 | DU | DU | DU | DU | DU | DU | | | | | | |
| 8 | DU | DU | DU | DU | DU | | | | | | | |
| 9 | DU | DU | DU | DU | | | | | | | | |
| 10 | DU | DU | DU | | | | | | | | | |
| 11 | DU | DU | | | | | | | | | | |
| 12 | DU | | | | | | | | | | | |

Rows correspond to the number of DLTs;
Columns correspond to the number of patients;
E: Escalate to the next higher dose;

# The Ji3+3 design for Eff-Tox Dose Finding



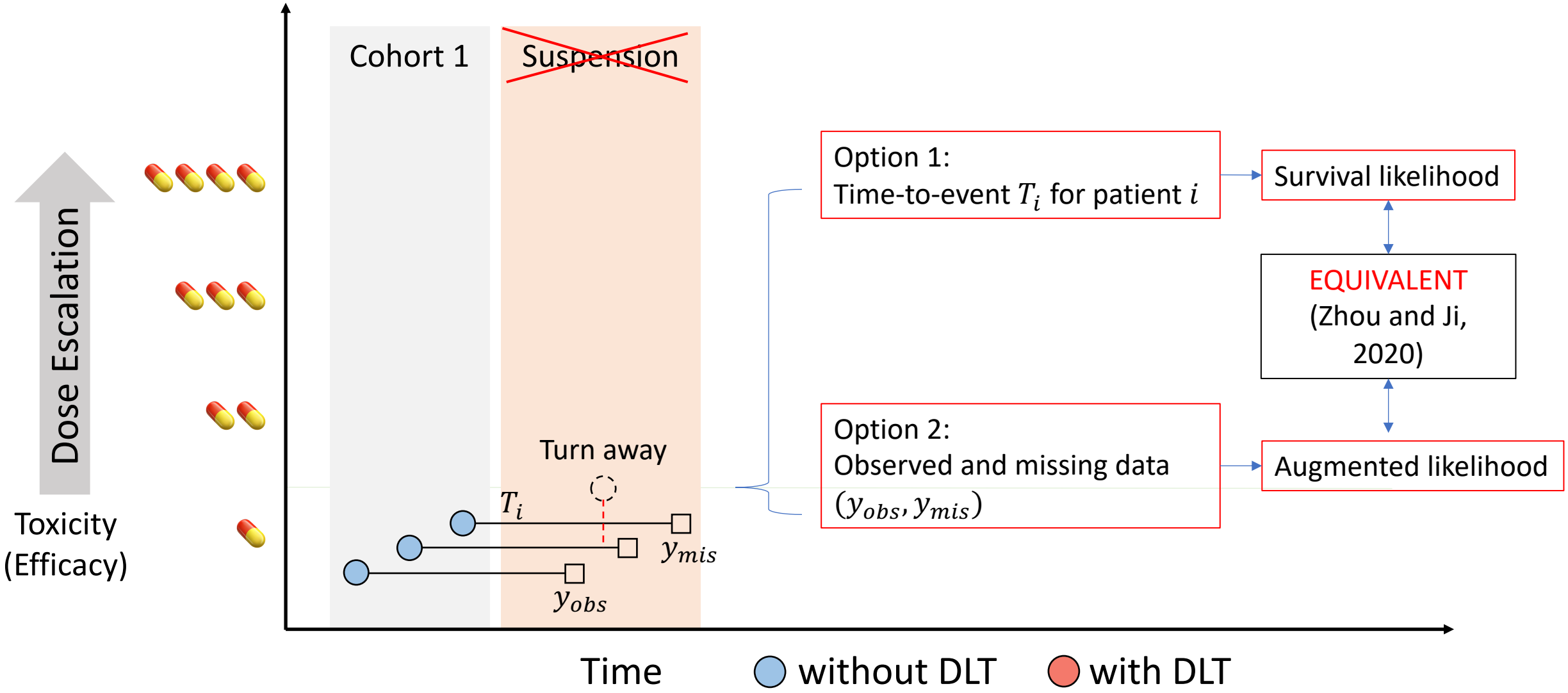

**At dose $d$,**
**$y$ patients have DLT,**
**x respond, out of**
**$n$ patients treated**

D (S)

$$\frac{y-1}{n} > p_T - e_1 \ (\frac{y-1}{n} < p_T - e_1)$$

# Statistical framework for modeling TITE Toxicity

To speed up the trial with “rolling enrollment”; i.e., no suspension always



# Examples of PoD Designs

**Reference** 1:

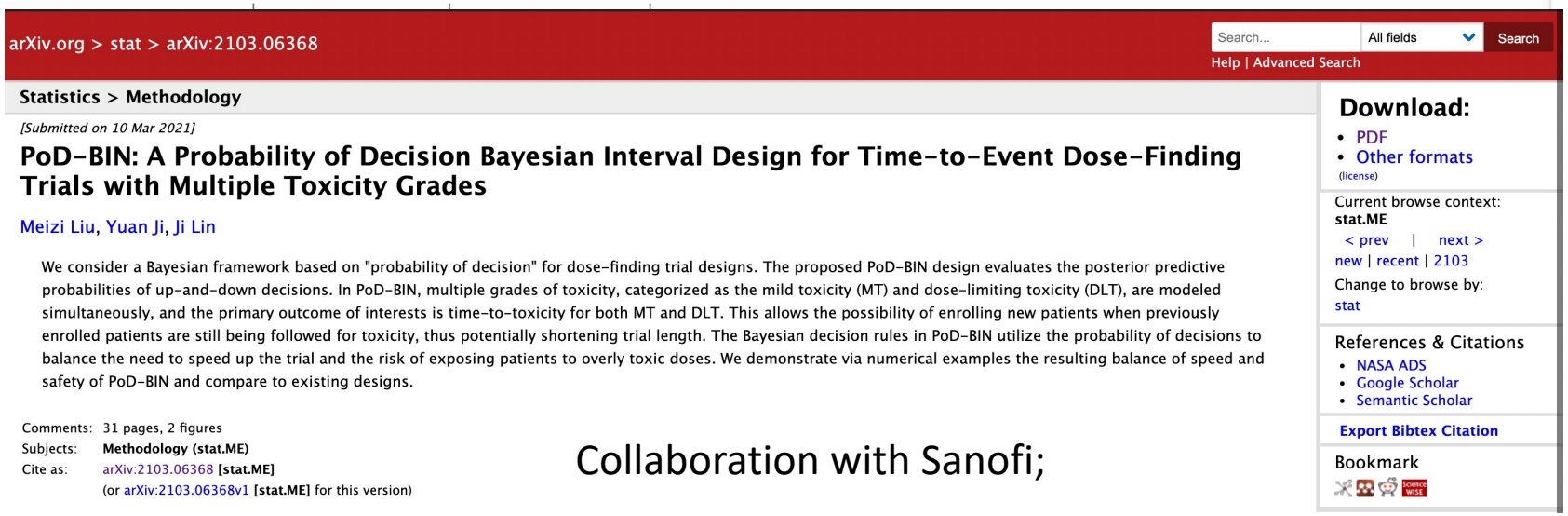
Published: 14 December 2019

## PoD-TPI: Probability-of-Decision Toxicity Probability Interval Design to Accelerate Phase I Trials

Tianjian Zhou, Wentian Guo & Yuan Ji

*Statistics in Biosciences* **12**, 124–145(2020) | Cite this article

**Reference** 2:



arXiv.org > stat > arXiv:2103.06368

Search... All fields Search

Help | Advanced Search

**Statistics > Methodology**

*[Submitted on 10 Mar 2021]*

## PoD-BIN: A Probability of Decision Bayesian Interval Design for Time-to-Event Dose-Finding Trials with Multiple Toxicity Grades

Meizi Liu, Yuan Ji, Ji Lin

We consider a Bayesian framework based on "probability of decision" for dose-finding trial designs. The proposed PoD-BIN design evaluates the posterior predictive probabilities of up-and-down decisions. In PoD-BIN, multiple grades of toxicity, categorized as the mild toxicity (MT) and dose-limiting toxicity (DLT), are modeled simultaneously, and the primary outcome of interests is time-to-toxicity for both MT and DLT. This allows the possibility of enrolling new patients when previously enrolled patients are still being followed for toxicity, thus potentially shortening trial length. The Bayesian decision rules in PoD-BIN utilize the probability of decisions to balance the need to speed up the trial and the risk of exposing patients to overly toxic doses. We demonstrate via numerical examples the resulting balance of speed and safety of PoD-BIN and compare to existing designs.

Comments: 31 pages, 2 figures
Subjects: **Methodology (stat.ME)**
Cite as: arXiv:2103.06368 **[stat.ME]**
(or arXiv:2103.06368v1 **[stat.ME]** for this version)

**Download:**
- PDF
- Other formats (license)

Current browse context: **stat.ME**
< prev | next >
new | recent | 2103
Change to browse by: stat

References & Citations
- NASA ADS
- Google Scholar
- Semantic Scholar

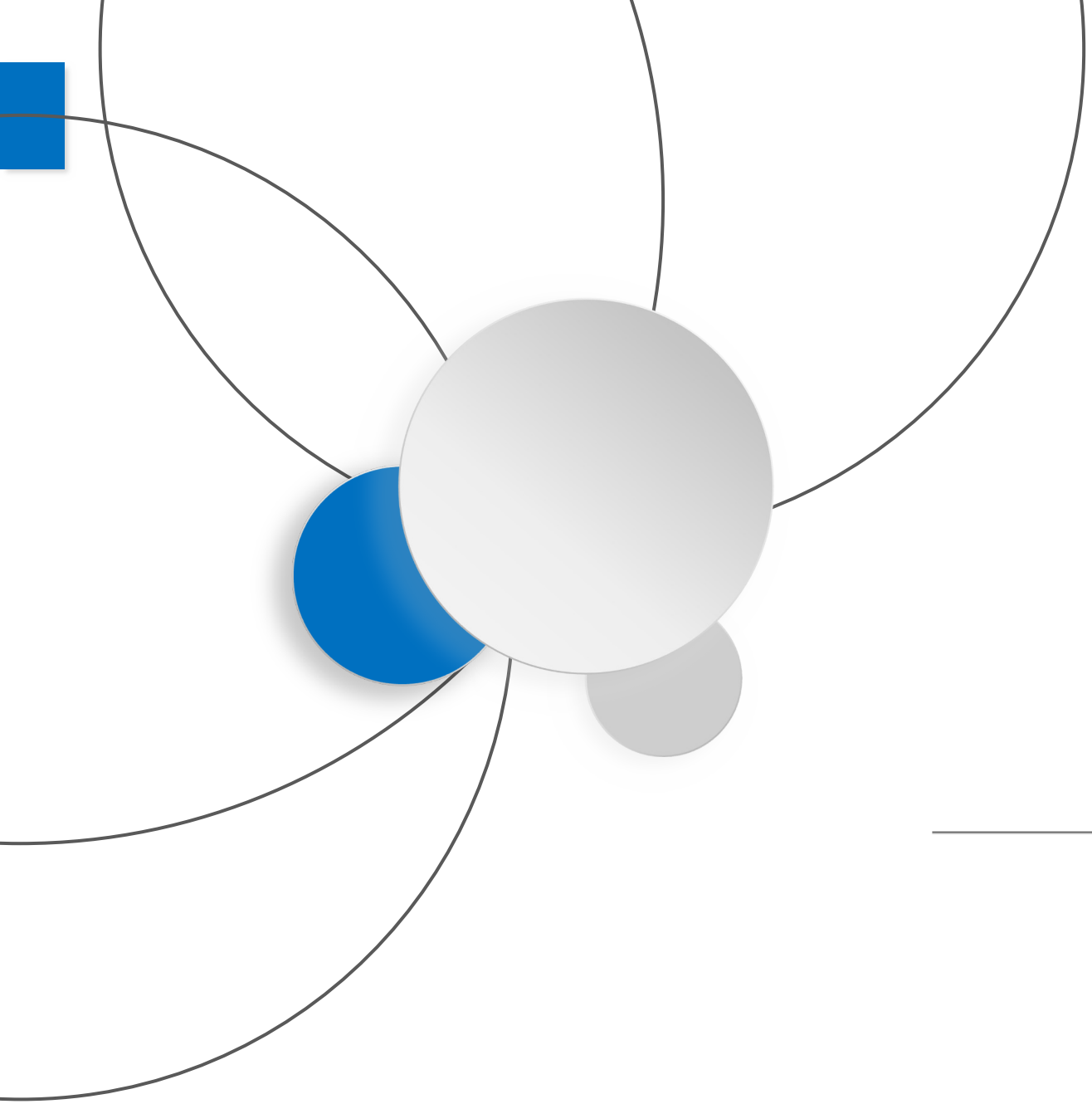
Export Bibtex Citation

Bookmark

Collaboration with Sanofi;

# Conclusion

- Many innovations have already been developed to meet the challenges of dose optimization
- They need to be tailored for practical trials and logistic requirement
- Oncology early-phase trials are getting more efficient but also more complex due to the innovation
- Overall, it benefits drug development and patients to have the innovation!



# Thank you!