Model-based, Model-assisted Designs for Early Phase Clinical Study: CRM, mTPI, Keyboard Design etc.

JungBok Lee
jungboklee@amc.seoul.kr
Department of Clinical Epidemiology & Biostatistics
ASAN Medical Center, Univ. of Ulsan College of Medicine

Definitions

- **Phase I trials:** formerly referred to as "first-in-man studies" but the field generally moved to the gender-neutral language phrase "first-in-humans" in the 1990s; these trials are the first stage of testing in human subjects. They are designed to test the safety, side effects, best dose, and formulation method for the drug. Phase I trials are not randomized, and thus are vulnerable to selection bias. (Wikipedia)

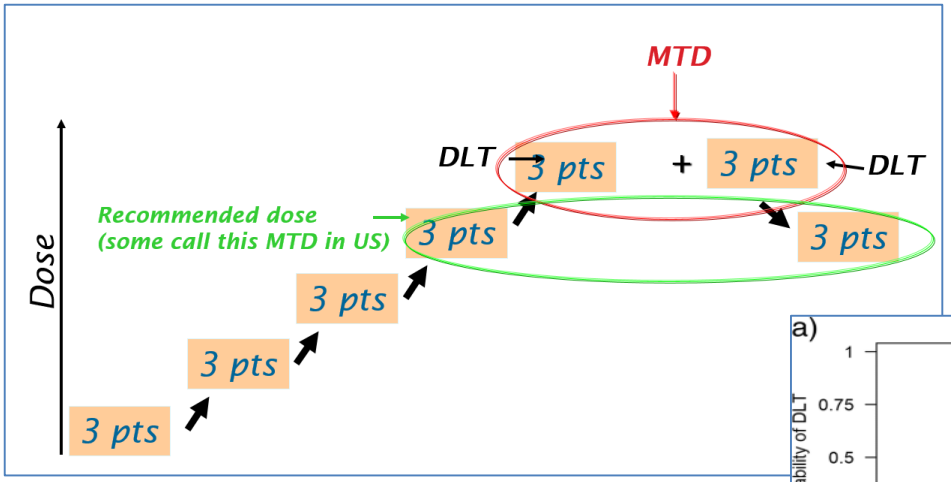
- **Dose-limiting toxicity (DLT):** Toxicity that is considered unacceptable (due to severity and/or irreversibility) and limits further dose escalation.

- **Maximum Tolerable Dose (MTD):** The highest dose of a drug or treatment that does not cause unacceptable side effects. The maximum tolerated dose is determined in clinical trials by testing increasing doses on different groups of people until the highest dose with acceptable side effects is found. Also called MTD.

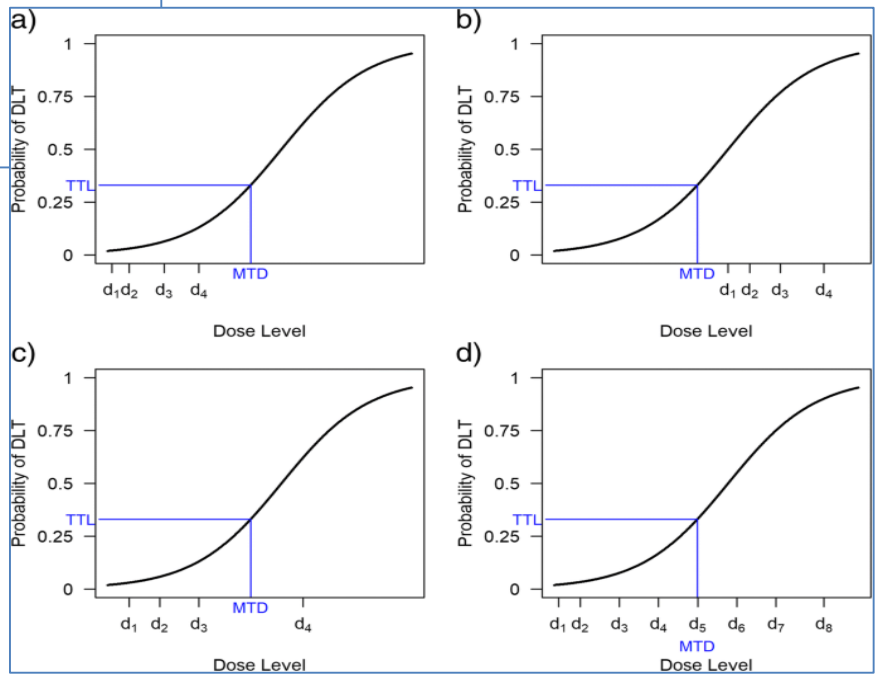
- Recommended phase II dose (RP2D, RD)

Methods

Standard 3+3

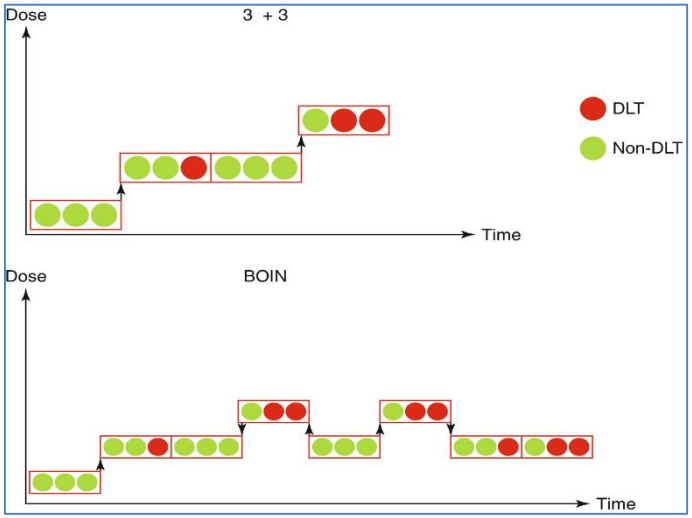


CRM

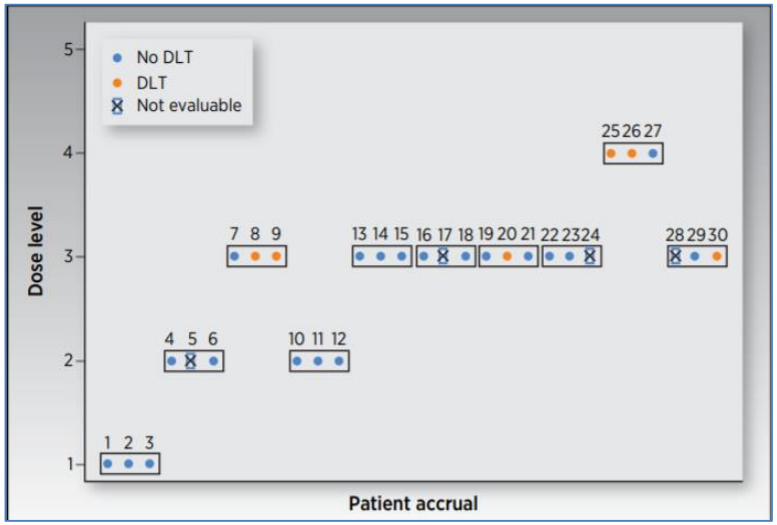


Methods

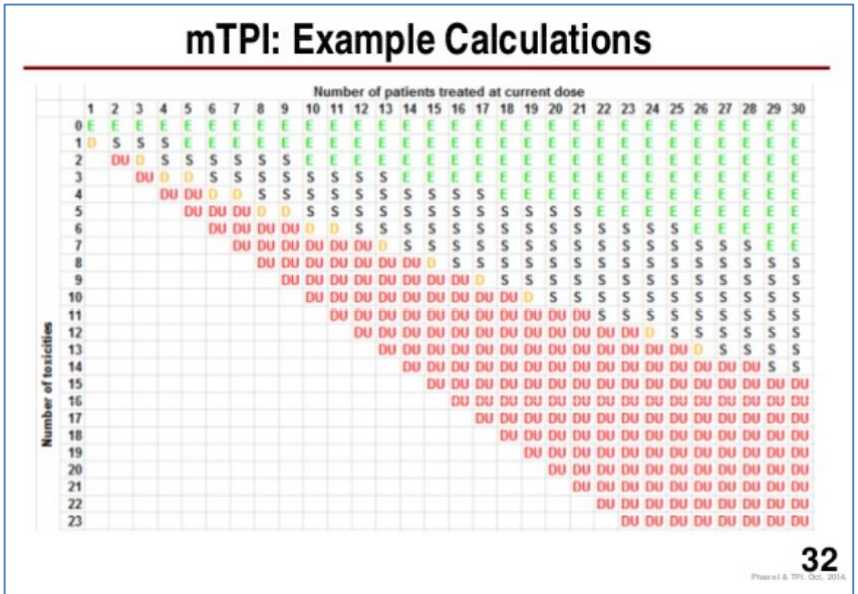
BOIN



Keyboard



mTPI



Classification-1

- Rule-based: 3+3, up & down method,
  accelerated titration design, mTPI, BOIN, keyboard
- Model-based: Continual Reassessment Method(CRM) & its extension

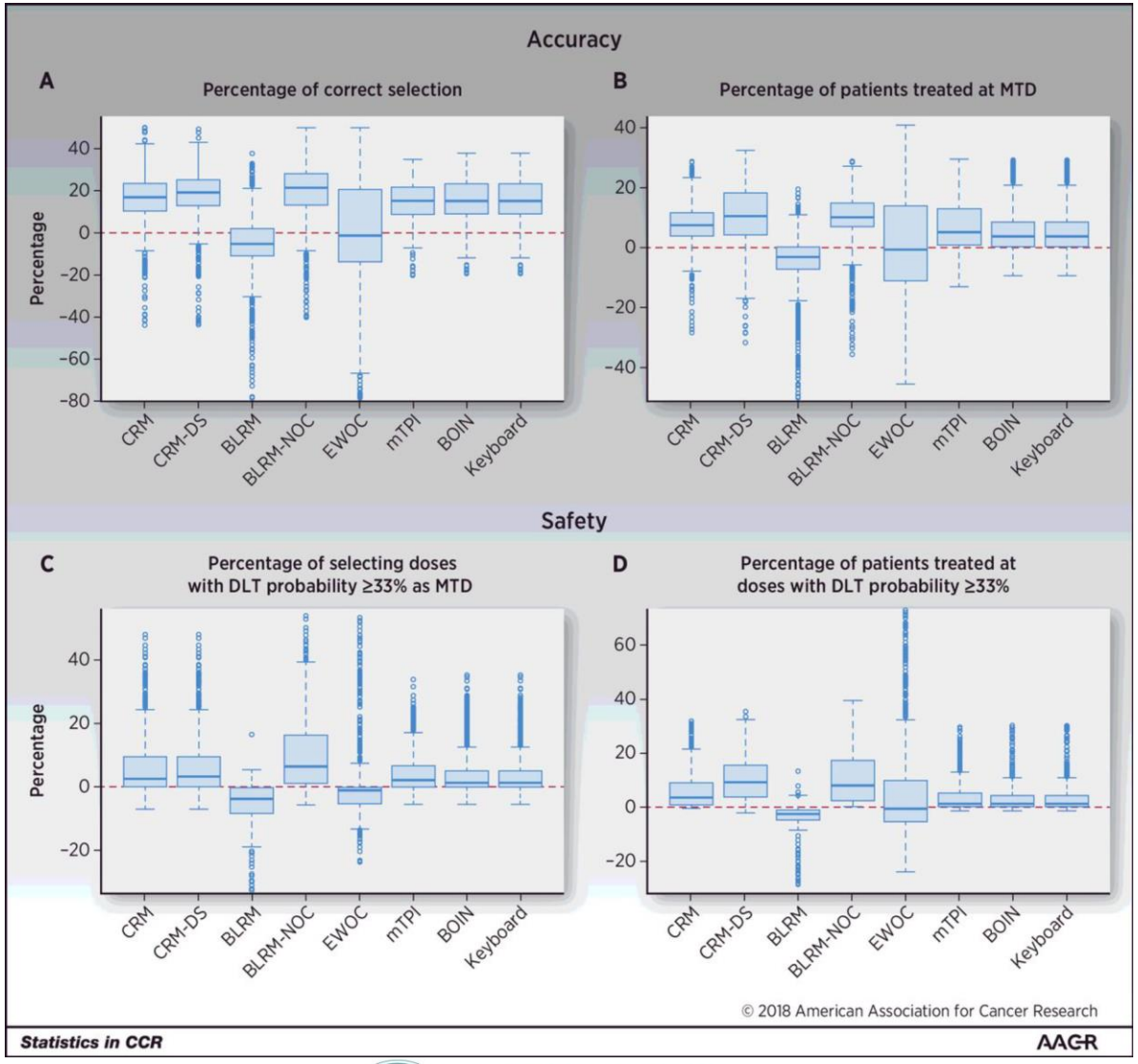
- **Algorithm-based**: a class of conventional design that uses a set of simple, prespecified rules to determine the dose escalation and de-escalation. (3+3, up&down, ATD)
- **Model-based:** a class of novel adaptive designs that uses a statistical model (eg, a logistic model) to describe the dose-toxicity curve and guide dose transition. (CRM & extension)
- **Model-assisted:** developed to combine the advantages of algorithm-based designs and model-based designs. Similar to the model-based design, the model-assisted design uses a statistical model (eg, the binomial model) to derive the design for efficient decision making; however, like the algorithm-based design, its dose escalation and de-escalation rule can be predetermined before the onset of the trial and, thus, can be implemented. in as simple a way as the algorithm-based designs. (mTPI, BOIN, Keyboard)

(Yuan et al, 2019, JCO)

Classification-2

Design Characteristic	Algorithm Based	Model Assisted	Model Based
Transparency and simplicity			
Dose escalation/de-escalation rule can be predetermined and included in the protocol	Yes	Yes	No
Avoids computation-intensive, repeated estimation of the dose-toxicity curve model to make interim decisions	Yes	Yes	No
Flexibility			
Targets any prespecified DLT rate	No	Yes	Yes
Allows decision making when the cohort size deviates from the planned size	No	Yes	Yes
No. of patients treated at the MTD can be > 6	No	Yes	Yes
Sample size can be calibrated to ensure good operating characteristics	No	Yes	Yes
Performance			
Identifies the MTD accurately	No	Yes	Yes
Allocates a high percentage of patients to the MTD	No	Yes	Yes
Provides good overdose control	Yes	Yes	Yes

Comparison



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Zhou et al.(2018, CCR)

Model-based:
CRM

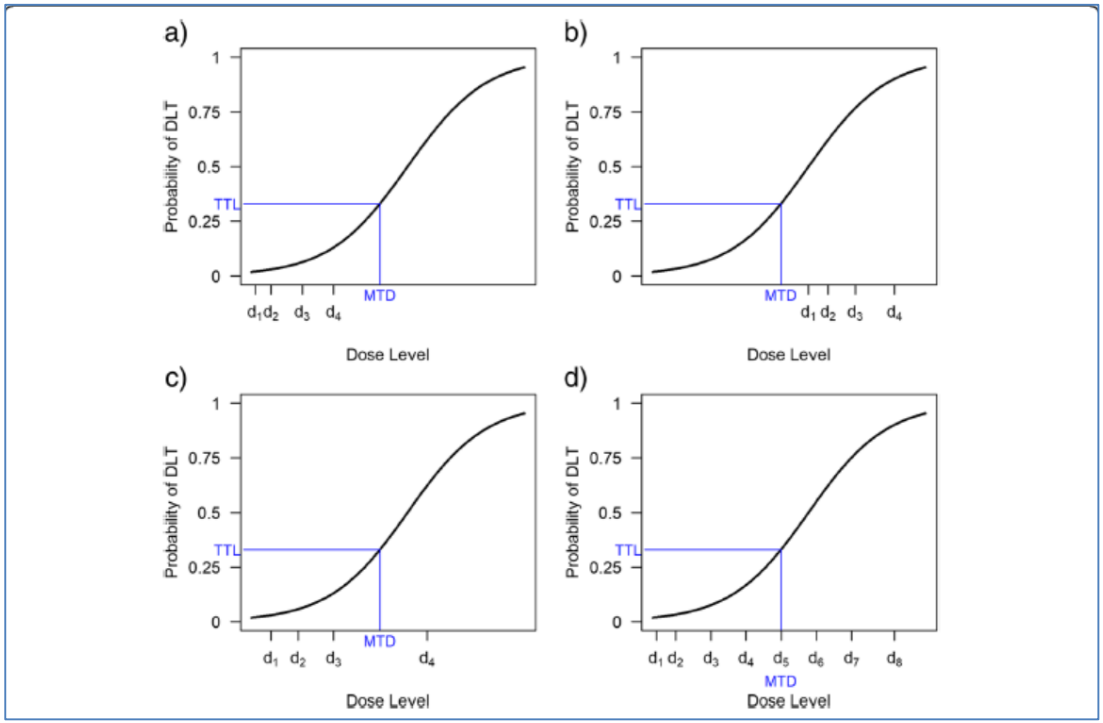
Continual Reassessment Model (CRM)

- This model-based Bayesian method was introduced by J. O'Quigley Biometrics 1990.

- A working model is specified for the dose-outcome relationship
- Prior information is required
- Then the study begins by dosing the first person at the "best" dose
- The analysis is updated given the data obtained
- For the next patient pick the "best" dose and continue
- Sample size generally fixed at the outset (20-30 pts)

Parameters to Set Up

- Target Toxicity Rate: The acceptable chance of a patient experiencing a DLT
- # of Doses (K): Statistical and practical considerations underlie the choice of how many and which doses to study.



Wheeler et al.(2019, BMC MRM)

Parameters to Set Up

- Dose-Toxicity Model: Relationship between dose and the risk of observing a DLT. The dose-toxicity model describes the probability of a patient experiencing a DLT at a given dose

Table 1 Common choices for dose-toxicity models and resultant dose labels for the CRM

Model name	Model ($F(\beta, d)$)	General form of dose labels (d_i)	Choice of β^* (prior mean or median)	Dose labels given β^* (d_i)
Power (empiric)	$d^{exp(\beta)}$	$p_i^{\frac{1}{exp(\beta)}}$	$\beta = 0$	p_i
One-parameter logistic	$\frac{exp(3+exp(\beta)\,d)}{1+exp(3+exp(\beta)\,d)}$	$\frac{\ln(\frac{p_i}{1-p_i})-3}{exp(\beta)}$	$\beta = 0$	$\ln(\frac{p_i}{1-p_i})-3$
Two-parameter logistic	$\frac{exp(\beta_1+exp(\beta_2)\,d)}{1+exp(\beta_1+exp(\beta_2)\,d)}$	$\frac{\ln(\frac{p_i}{1-p_i})-\beta_1}{exp(\beta_2)}$	$\beta_1 = 0, \beta_2 = 0$	$\ln(\frac{p_i}{1-p_i})$

Notation: p_i = skeleton probability of DLT at i^{th} dose level; d_i = dose label for for i^{th} dose level

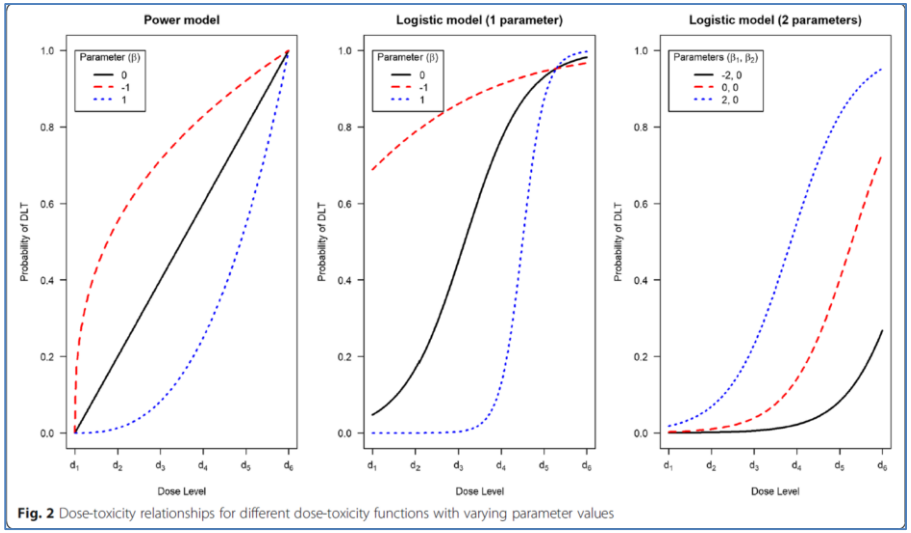


Fig. 2 Dose-toxicity relationships for different dose-toxicity functions with varying parameter values

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Update-1

- The dose-response curve: parameterized with slope β,

$$Pr(\text{Toxicity at level } d_k) = F(d_k, \beta)$$

- The current dose d_n is chosen such that

$$F(d_n, \beta) \leq p \text{ and } F(d_k, \beta) > p$$

for all $k > n$,
where p is the toxicity level
which defines the MTD.
(skeleton, initial guess)

Update-2

$$P(H|E) = \frac{P(E|H)P(H)}{P(E)}$$

사전 확률 (prior)

사후 확률 (posterior)

Given initial uncertainty about the parameter a, or
approach to the trial design. Three distinct approaches
distribution, including the use of analytically tractable
exponential density), the use of pseudo-data prior, an
prior are discussed in O'Quigley and Conaway [89]. The original CRM is fully sequential. The first patient is treated at the dose which a priori is thought to be closest to the MTD. Any subsequent patient is treated at a dose with estimated toxicity probability closest to the target toxicity level. Let $g(a)$ denote the prior density and let $\mathcal{F}_j = \{(x_1, y_1), \ldots, (x_j, y_j)\}$ denote the history from first j patients in the trial, where $x_m \in \{d_1, \ldots, d_K\}$ is the dose assignment and y_m is the toxicity outcome of the mth patient $(m = 1, \ldots, j)$. Using Bayes formula, the posterior density for a is $g(a|\mathcal{F}_j) = C^{-1}\mathcal{L}_j(a)g(a)$, where $\mathcal{L}_j(a) = \prod_{m=1}^{j}\{\psi(x_m, a)\}^{y_m}\{1 - \psi(x_m, a)\}^{1-y_m}$ is the binomial likelihood and $C = \int_0^\infty \mathcal{L}_j(a)g(a)da$ is the normalizing constant. The posterior mean toxicity probability at d_i is estimated as

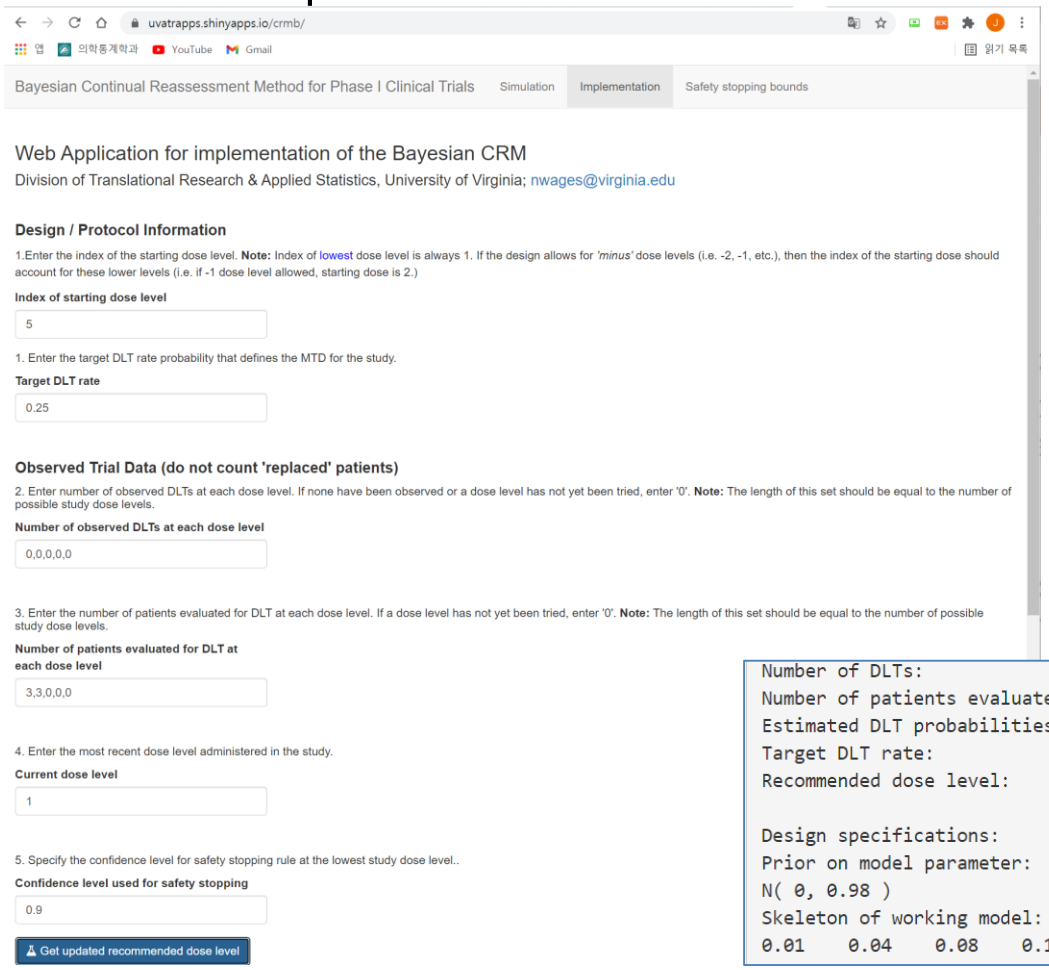
$$E_a\{\psi(d_i, a)|\mathcal{F}_j\} = \int_0^\infty \psi(d_i, a)g(a|\mathcal{F}_j), \quad i = 1, \ldots, K. \tag{3.2}$$

Then the dose assignment for the $(j+1)$th patient is determined as

$$X_{j+1} = \arg\min_{1 \le i \le K} |E_a\{\psi(d_i, a)|\mathcal{F}_j\} - \Gamma|. \tag{3.3}$$

Example

- Initial Step

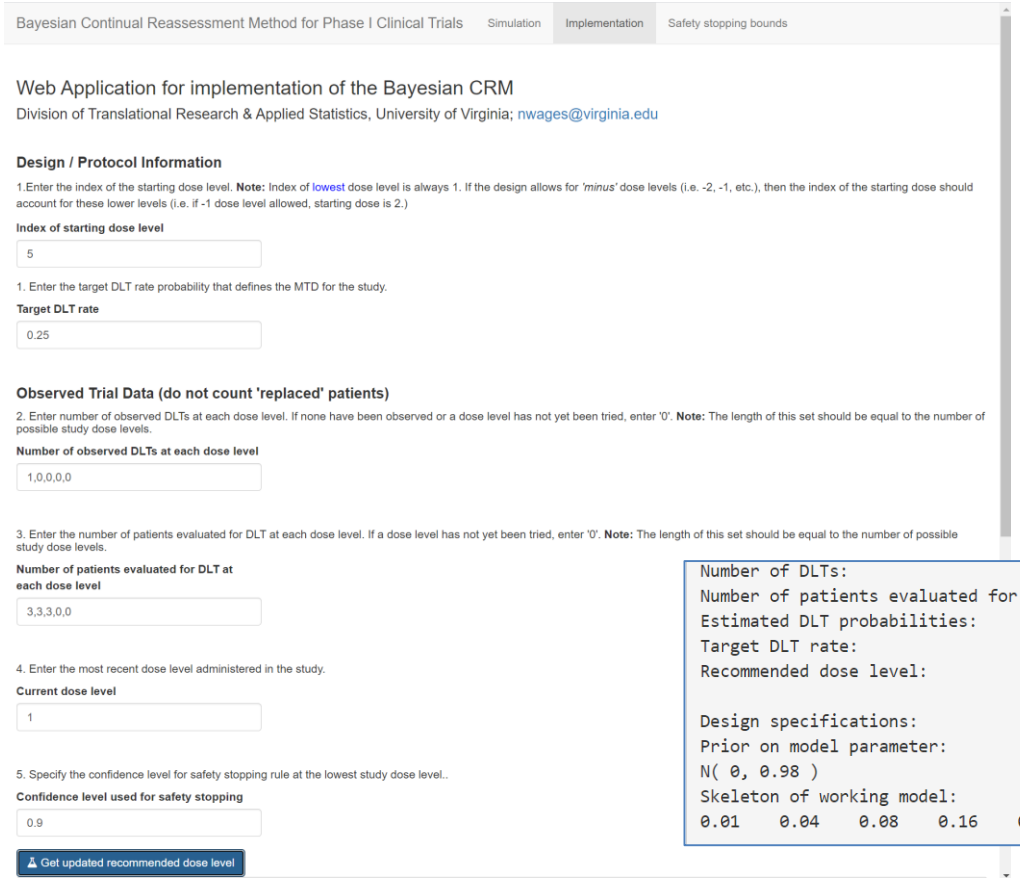


Number of DLTs:	0	0	0	0	0
Number of patients evaluated for DLT:	3	3	0	0	0
Estimated DLT probabilities:	0	0.01	0.02	0.05	0.11
Target DLT rate:	0.25				
Recommended dose level:	2				

Design specifications:
Prior on model parameter:
N(0, 0.98)
Skeleton of working model:
0.01 0.04 0.08 0.16 0.25

Example

- 1st Dose




```
Number of DLTs:                          1     0     0     0     0
Number of patients evaluated for DLT:    3     3     3     0     0
Estimated DLT probabilities:             0.06  0.12  0.21  0.31  0.42
Target DLT rate:                         0.25
Recommended dose level:                  2

Design specifications:
Prior on model parameter:
N( 0, 0.98 )
Skeleton of working model:
0.01    0.04    0.08    0.16    0.25
```

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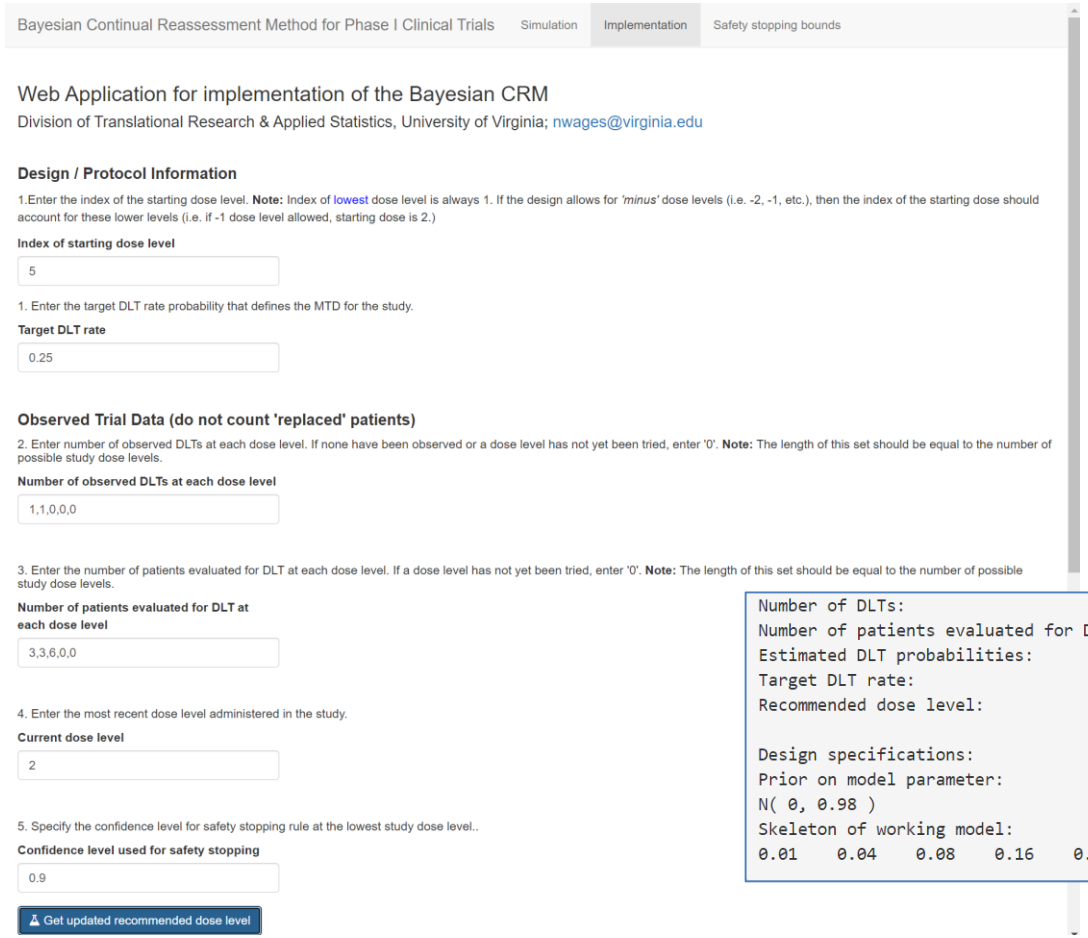
Example

- 2nd Dose



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Practical Issues

- Clinical Parameters

- Initial Guess of Toxicity Probability
- Prior MTD, Starting Dose
- Prior Distribution
- Dose-Toxicity Model
- Initial Design
- Sample Size

- Stopping Rule
- Calibration of Indifferent Interval
- etc

Model-assisted: mTPI & Keyboard (cf: mTPI-2)

TPI & mTPI (Ji et al. 2007, 2010)

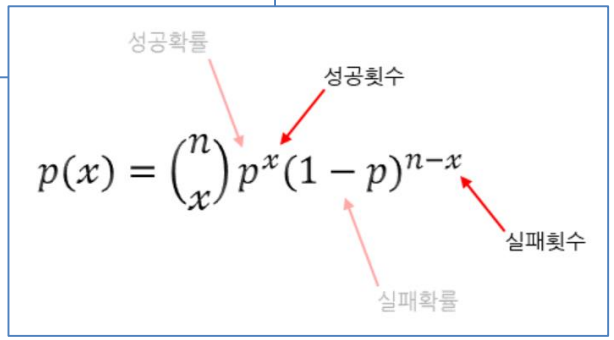
- Toxicity Probability Interval (TPI) method consists of two components: a beta/binomial model and a dose-assignment rule based on posterior toxicity probabilities.

- First, we adapt a conjugate beta/binomial Bayesian model that gives us closed-form beta posterior distributions for the dose toxicity probabilities.

Likelihood function is a product of binomial densities: $l(\boldsymbol{p}) \propto \prod_{i=1}^{d} p_i^{x_i}(1-p_i)^{n_i-x_i}$, where n_i and x_i are the numbers of patients treated at dose i and experienced DLT, respectively.

The priors of p_i are i.i.d. Beta(α, α), where α takes a small value, e.g., $\alpha = 0.005$, resulting in a U-shaped prior.

Posteriors are beta with known parameter values.



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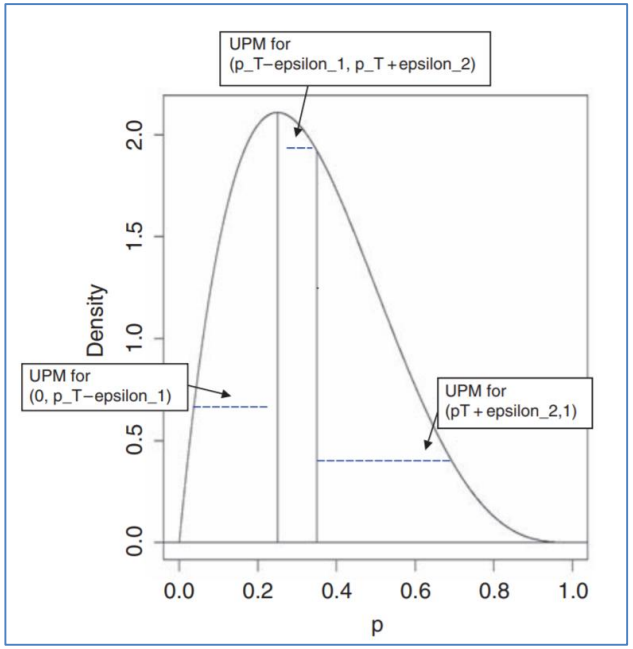
TPI

- Secondly, using the beta posteriors, we compute posterior probabilities of **three toxicity intervals** that are associated with high, acceptable, and low toxicity for the dose at which patients are being treated; we associate each interval with a different dose-assignment action for treating future patients



Let D, S, E denote the decision to de-escalate to dose $(i-1)$, stay at dose i, and escalate to dose $(i+1)$, respectively. Following the main idea, define the posterior probabilities for the three intervals:

$$q(D,i) = P(p_i - p_T > K_1\sigma_i|\text{data}),$$

$$q(S,i) = P(-K_2\sigma_i \le p_i - p_T \le K_1\sigma_i|\text{data}),$$

$$q(E,i) = P(p_i - p_T < -K_2\sigma_i|\text{data}).$$

The dose-assignment rule

$$\mathcal{B}_i = \arg \max_{m\in\{D,S,E\}} q(m,i),$$

mTPI

- mTPI introudced a set of **penalty functions** for choosing a proper decision from among D, S, or E.
- The mTPI is based on a new statistics called the **unit probability mass**.

- The mTPI improves the TPI on two aspects:
- mTPI is calibration free – does not require tuning of parameters
- mTPI is safer – treats fewer patients at over-toxic doses while maintaining other good performance properties of the TPI.

At MD Anderson

Software Download Kiosk > Toxicity Probability Intervals

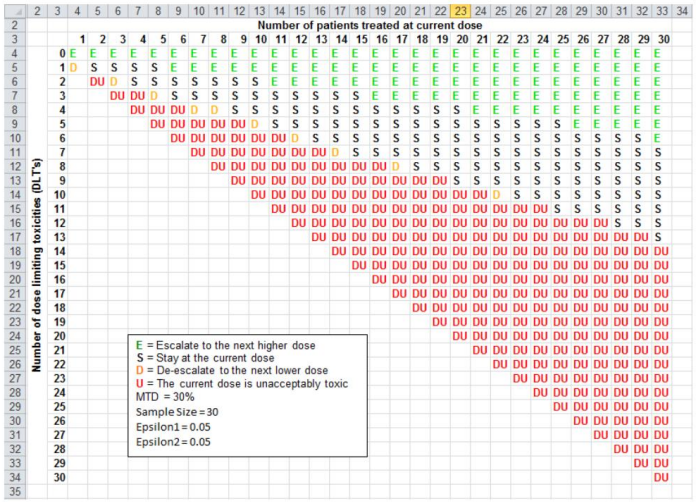
Version 2.1, Last Modified Date: 10/5/2012

Download	File Name	File Size in KB	Notes
	TPI_V2.1PID439.zip	5545	Zip file containing manuscript, Excel files, and R code.

Toxicity Probability Intervals

This software implements the method described in "Dose-Finding in Oncology Clinical Trials Based on Toxicity Probability Intervals" by Yuan Ji, Yisheng Li, and Nebiyou Bekele. This application uses a Microsoft Excel macro to produce a table that can be used to conduct the trial. An Excel addin and macros are also provided to perform simulations, as well as R scripts for generating both the table and performing simulations.

The addin operates in Microsoft Excel 2010 or 2007, running under Windows 7.



Please note that to run the software as an Excel macro, your macro security must be set to "Medium" or "Low". To do this, open Excel, click on Tools, select Macro from the drop-down list, and click Security. Set the security level to "Medium" or "Low" in the pop-up window by clicking the button in front of the desired level. Once you have selected your desired security level, click OK and close Excel. You are now ready to open this macro. Once the macro is opened, a smiley-face icon will appear in the toolbar. Clicking on the icon will run this macro. If your security level is already set to "Medium" or "Low", the smiley-face icon will appear automatically. See the **mTPI_ReadMe.doc** document in the zip file for additional instructions.

See the manuscript describing the method: A Modified Toxicity Probability Interval Method for Dose-Finding Trials by Yuan Ji, Ping Liu, Yisheng Li, and B. Nebiyou Bekele.

Software developed by Yuan Ji and Richard Herrick.

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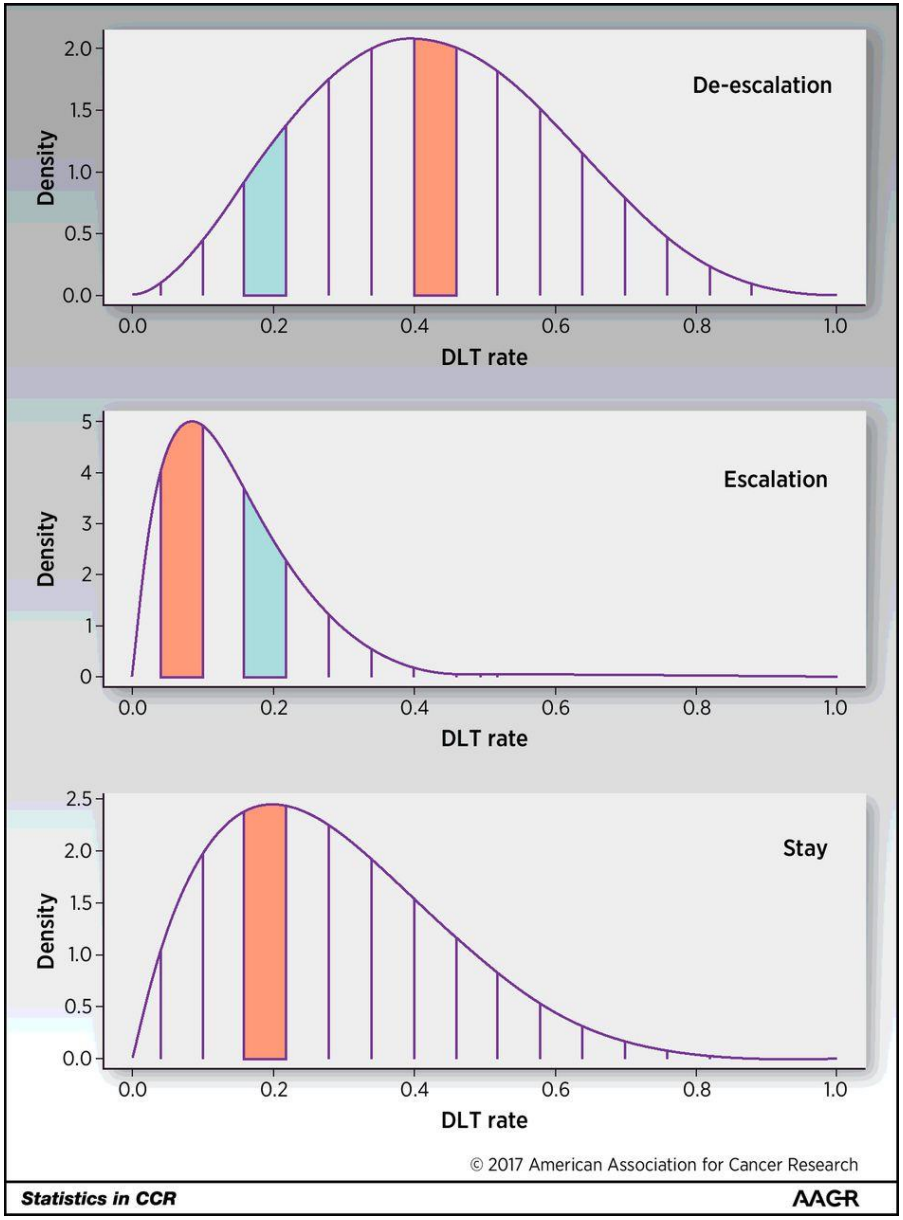
Keyboard Design (Yan et al, 2017, CCR)

- The keyboard design retains the simplicity of the mTPI design, but yields better overdose control and higher accuracy to identify the true MTD.

- Similar to the mTPI design, the keyboard design is a Bayesian model-based design that relies on the posterior distribution of the toxicity probability to guide dose escalation and de-escalation.

- The innovation is that the keyboard design defines a series of equal-width dosing intervals (or **keys**) to present the potential locations of the true toxicity of a dose and guide the dose escalation and de-escalation, whereas the mTPI design uses the **UPM**s of three dosing intervals (i.e., underdosing, proper dosing, and overdosing) to determine the dose transition

- CF: "strongest" key that has the highest posterior probability.



- If the strongest key (red) is on the right side of the target key (blue), de-escalate the dose (top);
- if the strongest key is on the left side of the target key, escalate the dose (middle);
- if the strongest key is the target key, retain the current dose (bottom).

Implement-1

1.	Start the trial by treating the first patient or the first cohort of p atients at the lowest dose.
2.	To choose a dose for treating the next new patient, count the n umber of DLTs observed at the current dose and conduct dose escalation and de-escalation based on the pretabulated decisio n rules.
3.	Repeat step 2 until the prespecified maximum sample size is rea ched or the trial is terminated early for safety.
4.	On the basis of all the observed data, select the MTD using a st atistical technique called isotonic regression (16).

Implement-2

Table 2.

Dose escalation and de-escalation rules for target DLT rates of 0.2 and 0.3 under the keyboard design

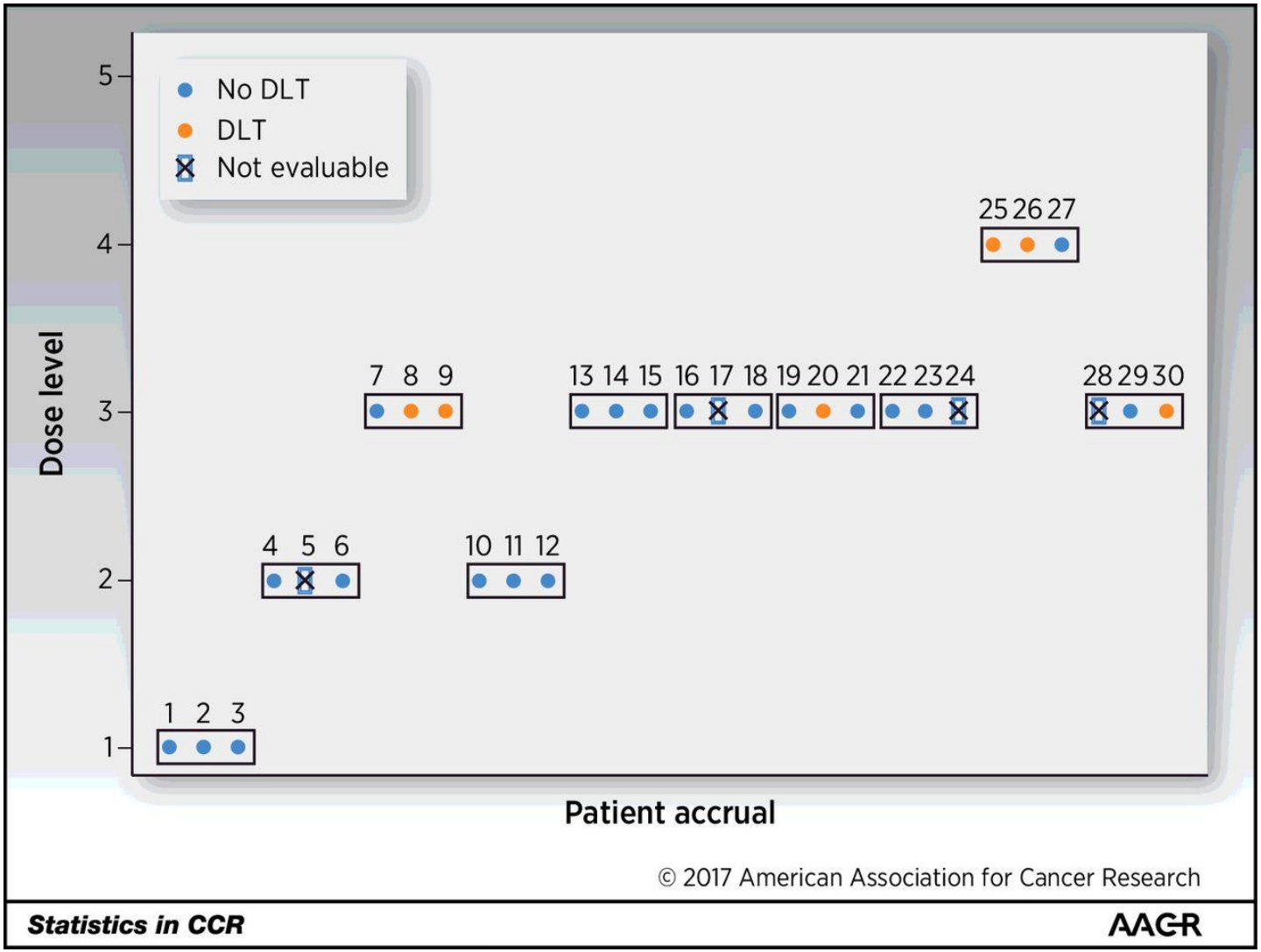
	The number of patients treated at the current dose																	
Action	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Target DLT rate = 20%[a]																		
Escalate if number of DLTs ≤	0	0	0	0	0	0	1	1	1	1	1	1	1	2	2	2	2	2
De-escalate if number of DLTs ≥	1	1	1	1	2	2	2	2	3	3	3	3	3	4	4	4	4	5
Eliminate if number of DLTs ≥[b]	NA	NA	2	3	3	3	4	4	4	5	5	5	5	6	6	6	7	7
Target DLT rate = 30%[a]																		
Escalate if number of DLTs ≤	0	0	0	0	1	1	1	1	2	2	2	2	3	3	3	3	4	4
De-escalate if number of DLTs ≥	1	1	2	2	2	3	3	3	4	4	4	5	5	5	6	6	6	7
Eliminate if number of DLTs ≥[b]	NA	NA	3	3	4	4	5	5	5	6	6	7	7	8	8	8	9	9

Abbreviation: NA, not applicable.

[a]The proper dosing intervals are (15%, 23%) and (25%, 35%) for target DLT rates of 20% and 30%, respectively, as in the simulation study.

[b]When the current dose is eliminated from the trial, the higher doses should also be eliminated and the dose is automatically de-escalated to the next lower level for treating the next new patient. A minimum of three patients must be treated before a dose can be eliminated.

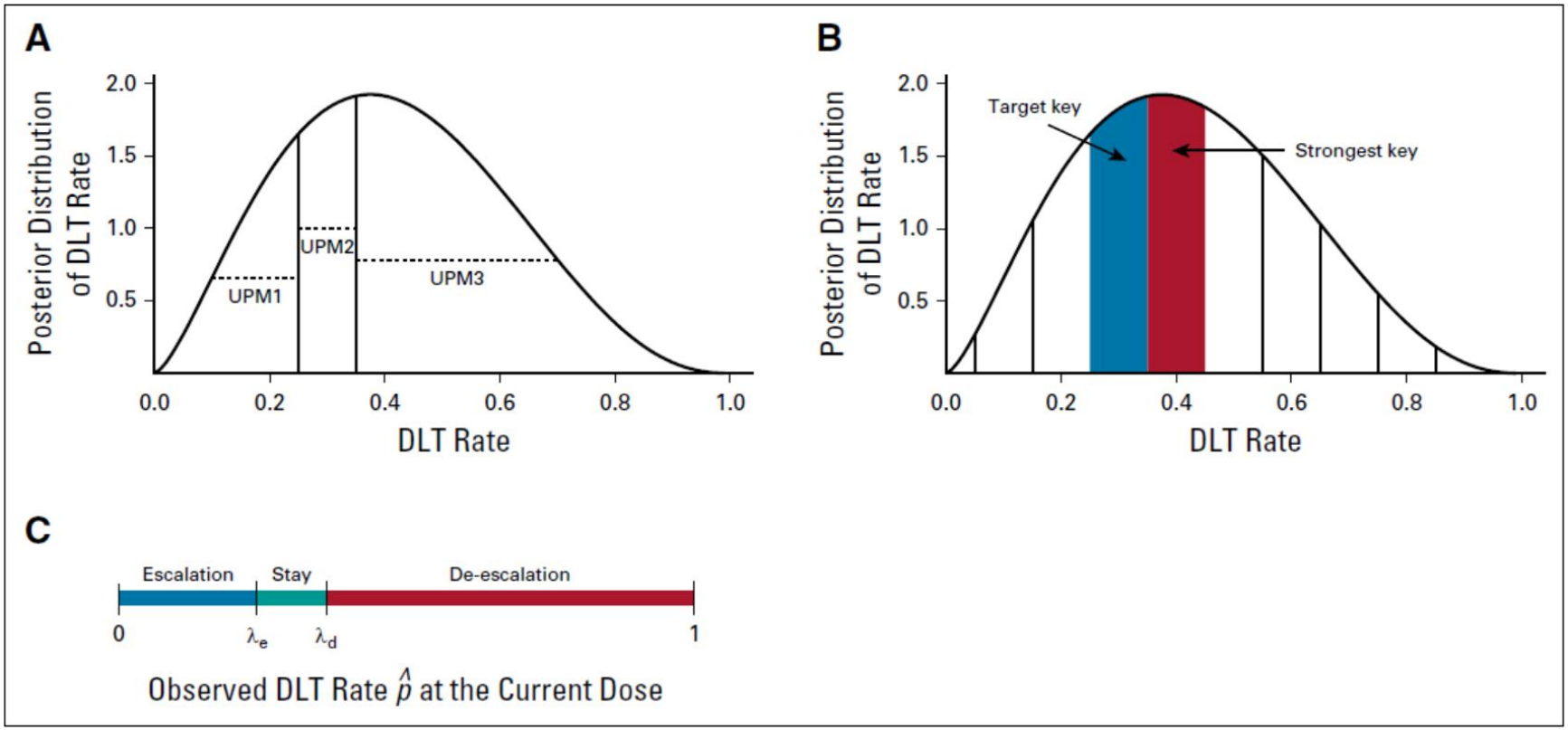
Implement-3



BOIN

- Refer Dr Gil's Talk

Summary: mTPI, Keyboard & BOIN



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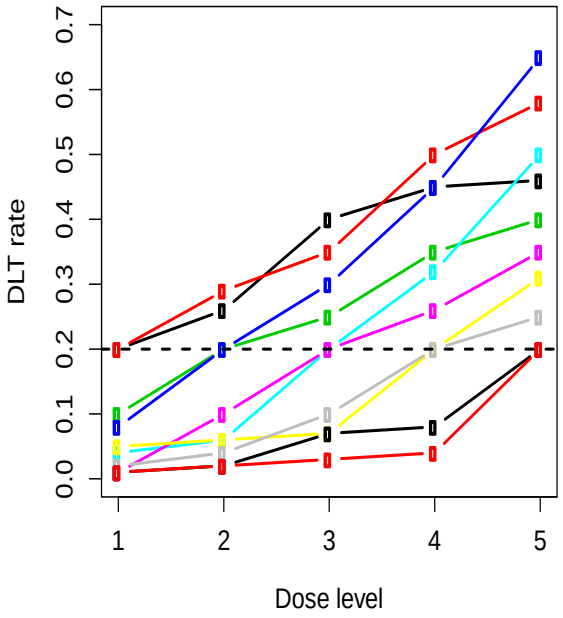
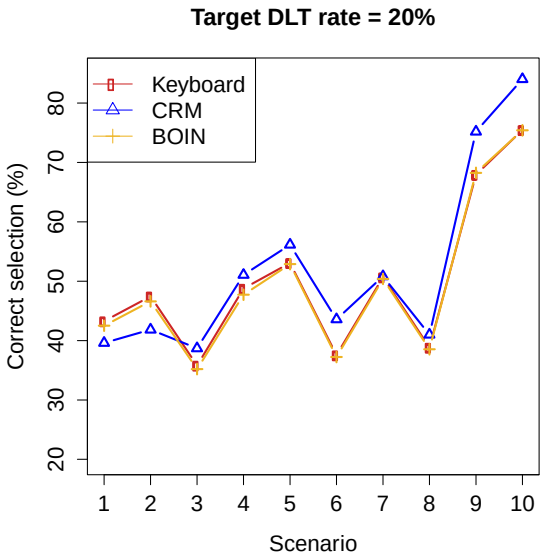
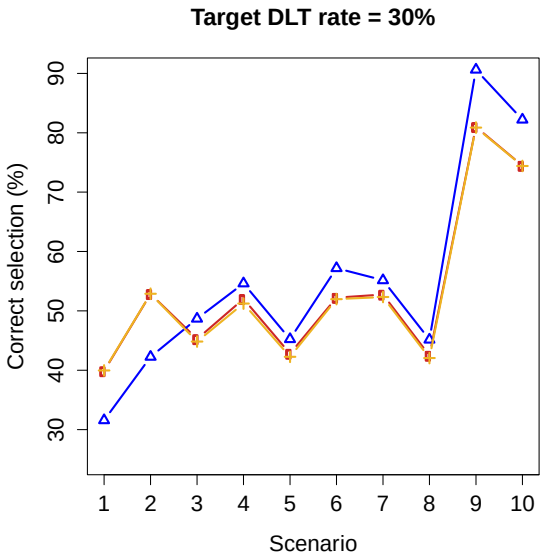
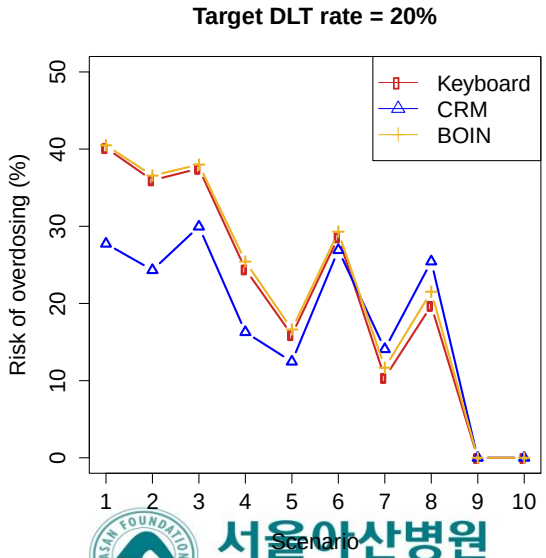
Comparison-1 (Yan et al. 2017, CCR)

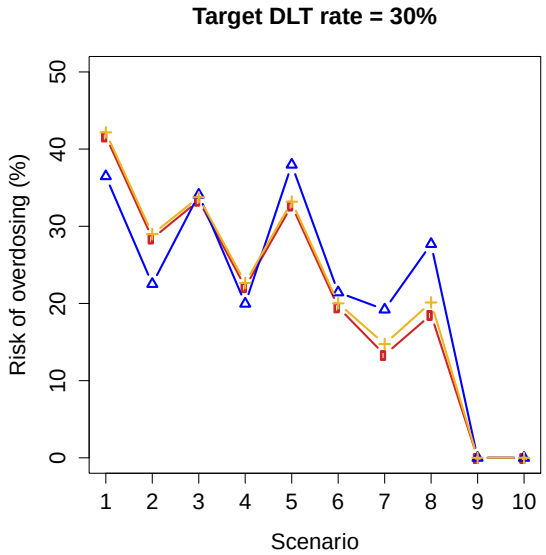
- From 10 Scienarios











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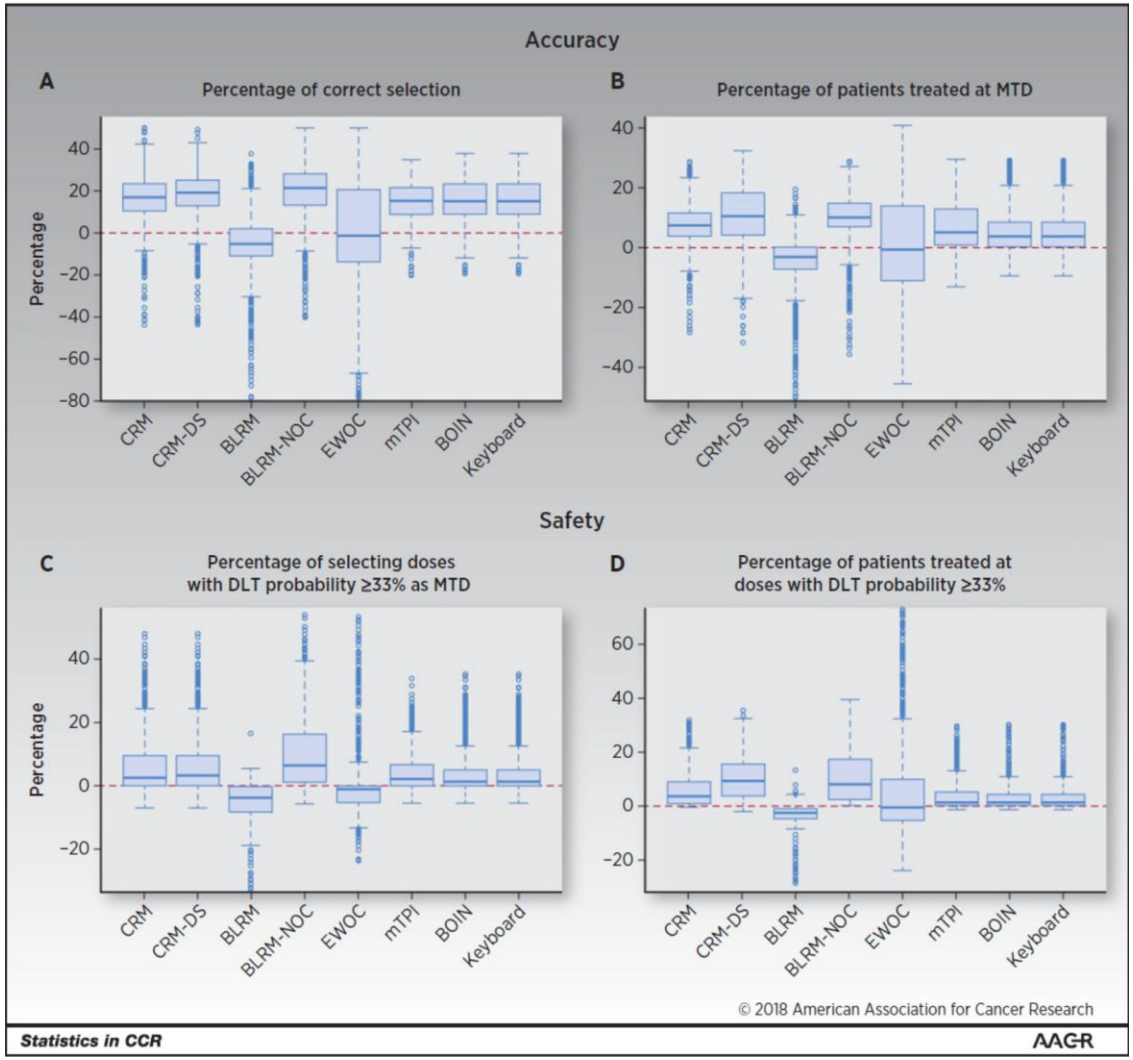
Comparison-2 (Zhou et al. 2018, CCR)



Relative difference of 3+3

For A,B Larger=better

For C,D Smaller=better

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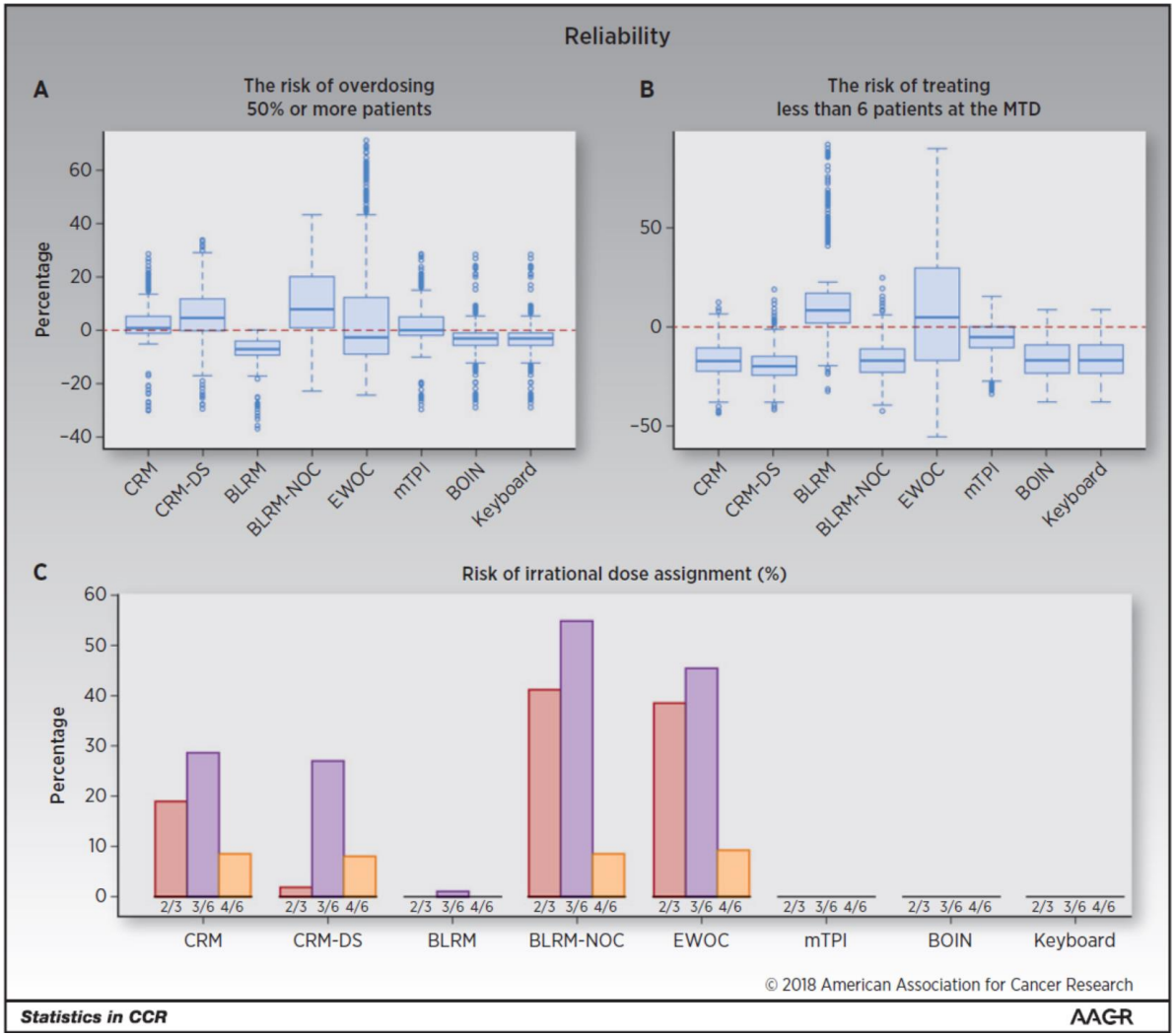
Comparison-3 (Zhou et al. 2018, CCR)



Relative difference of 3+3

Smaller=better

Comparsion-4
Zhu et al. (2019, Cont. Clincial Trials)

- In many cases CRM performs as well as or better than BOIN and Keyboard designs
- CRM is sensitive to the choice of prior toxicity probabilitie.
- The poor performance of CRM due to a misspecified prior may not be improved by simply increasing the sample size.
- Model-assisted designs performs well as the CRM, and also offer similar simplicity in implementation to the traditional 3+3 design.The advantage of the CRM is that it can be more efficient than the BOIN and Keyboard because it utilizes all available information.

Issues in Conducting

- Computational Resources including human resources
- Operational Burdens: not cohort of pts, but fully sequential
- Data Management
- Advantages of Model-assisted methods in case of small dose levels (3-4 doses) (typical in Korea, not newly developed drugs)

Thank you!!

jungboklee@amc.seoul.kr

서울아산병원
Asan Medical Center