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Bayesian Optimal Interval (BOIN) Design

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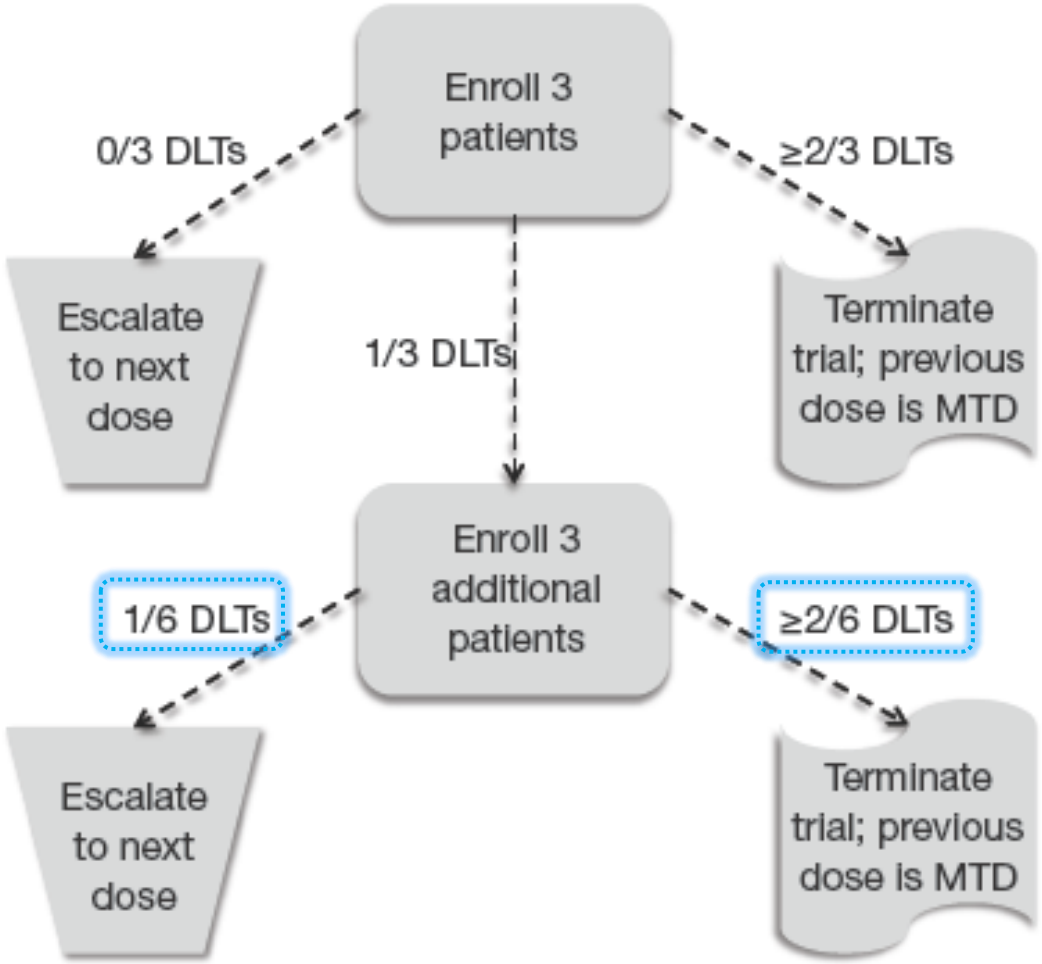
What will be discussed

- 3+3 Design vs. Bayesian Optimal Interval(BOIN)
- BOIN dose transition and MTD selection rule
- BOIN example trial and simulation result
- BOIN software 사용과 프로토콜 기술

The 3+3 Design



- Rule based design
- Statistical Models 에 기반하지 않음
  - 직관적이고 간단하다
  - Clinicians 과 Investigator 들이 잘 이해하고 있는 Traditional 한 방법
- 관측된 DLT 추정치를 기반으로 용량 증가/감소
- 1/6 (16.7%) 이상 1/3 (33.3%)이하의 Target DLT 추정

The 3+3 Design

Limitation

- 최저용량이 첫 코호트
- 바로 전 단계용량의 코호트를 제외하고 dosage history 를 이용하지 않음
- Re-escalate 불가
- Cohort size 가 3 또는 6으로 정해져 있으며 변동불가
- Target DLT 가 (16.7% ~ 33.3%) 을 벗어나는 상황이라면 MTD 추정불가
- 다른 방법들에 비하여 MTD 를 추정하는 정확도가 떨어지며 underdose 할 확률이 높음

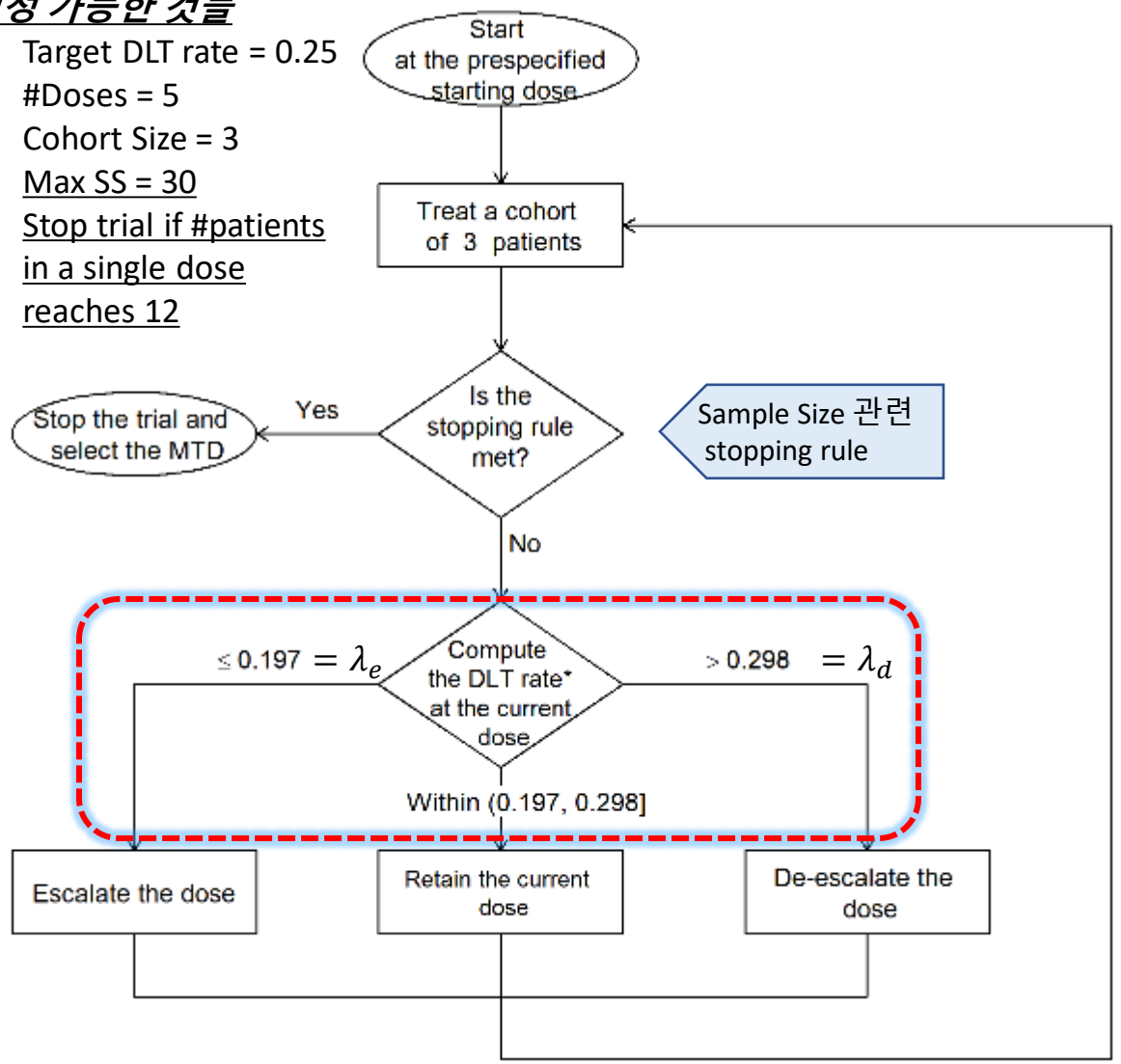
3+3 vs. BOIN

	3+3 Design	BOIN Design
Model	Rule Based	Model assisted design : 매 코호트 마다 업데이트되는 DTL 의 Posterior Probability 를 이용함
시작용량	최저 용량	선택가능
관측된 DLT 추정치	바로 전 단계용량 코호트와 다음 단계 코호트의 현재 정보(#DLT) 이용, dose history 이용하지 않음	현재 용량코호트에 배정된 모든 환자의 정보 (#DLT) history를 이용하여 DLT 추정
Re-escalate	불가	가능
Cohort size	변동 불가, 3 또는 6	설정가능, 또한 임상시험 진행 중 변동 가능
설정 가능한 Target DLT	1/6 (16.7%) < Target DLT < 1/3 (33.3%)	10% ≤ Target DLT ≤ 60%
MTD 추정의 정확도	Model assisted 또는 Model based design 에 비하여 떨어짐	3+3 Design 에 비하여 정확도 높음
전체시험대상자수 설정	불가	가능

The BOIN Design - *S. Liu and Y. Yuan (2015)*

설정 가능한 것들

- Target DLT rate = 0.25
- #Doses = 5
- Cohort Size = 3
- Max SS = 30
- Stop trial if #patients in a single dose reaches 12



- **Model assisted design**

  :Inference 는 point estimate 기반이며 간단한 모델로 부터 계산됨

- **관측된 DLT rate 추정치 ($\hat{p}$)**

$$\hat{p} = \frac{\text{현재 용량에서 } DLT \text{ 를 경험한 모든 환자수}(\boldsymbol{m_j})}{\text{현재 용량에 배정된 모든 환자수}(\boldsymbol{n_j})}$$

$$\begin{cases} \text{if } \hat{p} \le \lambda_e, \text{ then escalate the dose} \\ \text{if } \hat{p} > \lambda_d, \text{ then de-escalate the dose} \\ \text{otherwise, retain the dose} \end{cases}$$

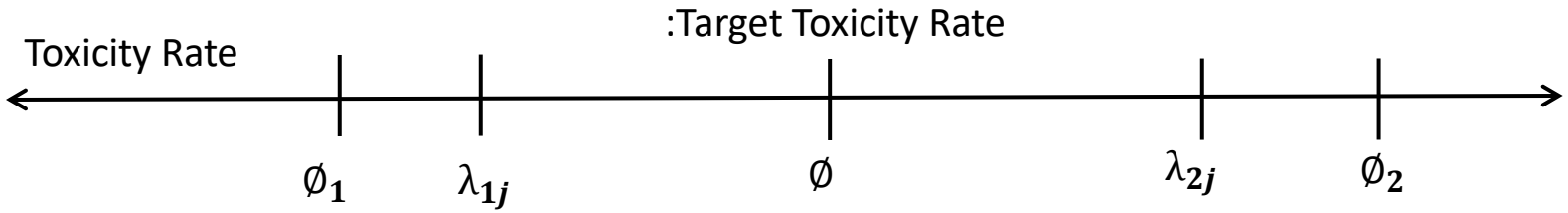
- **Question:** BOIN 의 DLT 추정치에 기반한 dose transition rule (λ_e, λ_d)은 어떻게 결정되는가?

BOIN - dose transition rules based on the point estimate ($\hat{p}$)

- BOIN : Bayesian Optimal Interval
- Interval design 에서 Interval boundaries, (λ_e, λ_d) 은 디자인의 운영상 특징을 결정하므로 매우 중요하며 이 boundaries 는 incorrect decision 을 최소화 하는 값(optimization) 으로 결정됨
- 각 용량 단계 (j) 마다 3개의 point(local) hypotheses 를 설정함

	$H_1: p_j = \emptyset_1$ 현재 용량은 subtherapeutic 하므로 용량 증가 필요	$H_0: p_j = \emptyset$ 현재 용량이 MTD	$H_2: p_j = \emptyset_2$ 현재 용량은 toxic 하므로 용량 감소 필요
Correct decision	E: Escalation (용량증가)	R: Retainment (용량유지)	D: De-escalation (용량감소)
Incorrect decision	R, D	E, D	E, R

BOIN - dose transition rules based on the point estimate ($\hat{p}$)



	$H_1: p_j = \emptyset_1$	$H_0: p_j = \emptyset$	$H_2: p_j = \emptyset_2$
Correct decision	E: Escalation	R: Retainment	D: De-escalation
Incorrect decision	R, D	E, D	E, R

$\underline{\emptyset_1, \emptyset, \emptyset_2}$: Physician 들이 정하는 값

$\underline{\lambda_{1j}, \lambda_{2j}}$: BOIN 이 optimize 한 값

$\emptyset_1 - \emptyset$: Target toxicity rate 보다 이 정도는 차이가 나야 practical 하게 의미 있는 차이라고 생각 되는 값. 이 값을 기반으로 decision error rate, $\lambda_{1j}, \lambda_{2j}$ 계산되며 sample size calculation 의 effact size 와 대응될 수 있는 개념

$$Decision\ Error\ Rate$$
$$Pr(Incorrect\ decision) = \mathrm{pr}(H_0)\,\mathrm{pr}(\mathrm{E\ or\ D}|H_0) + \mathrm{pr}(H_1)\,\mathrm{pr}(\mathrm{R\ or\ D}|H_1) + \mathrm{pr}(H_2)\,\mathrm{pr}(\mathrm{E\ or\ R}|H_2)$$
$$\alpha(\lambda_{1j}, \lambda_{2j})$$

↑ : Prior distribution,

⇡ : Binominal distribution 이용하여 표현됨

$$\lambda_{1j} = \frac{log\left(\frac{1-\emptyset_1}{1-\emptyset}\right) + n_j^{-1} log\left(\frac{\mathrm{pr}(H_1)}{\mathrm{pr}(H_0)}\right)}{log\left\{\frac{\emptyset(1-\emptyset_1)}{\emptyset_1(1-\emptyset)}\right\}} \qquad \lambda_{2j} = \frac{log\left(\frac{1-\emptyset}{1-\emptyset_2}\right) + n_j^{-1} log\left(\frac{\mathrm{pr}(H_0)}{\mathrm{pr}(H_2)}\right)}{log\left\{\frac{\emptyset_2(1-\emptyset)}{\emptyset(1-\emptyset_2)}\right\}}$$

Bayesian paradigm 안에서
Incorrect decision rate 을 최소화하는
$\lambda_{1j}, \lambda_{2j}$ 는 explicit 하게 표현 가능함.

Bayesian Optimal Interval boundaries

$$\lambda_{1j} = \frac{log\left(\frac{1-\emptyset_1}{1-\emptyset}\right)+n_j^{-1}log\left(\frac{\mathrm{pr}(H_1)}{\mathrm{pr}(H_0)}\right)}{log\left\{\frac{\emptyset(1-\emptyset_1)}{\emptyset_1(1-\emptyset)}\right\}} \qquad \lambda_{2j} = \frac{log\left(\frac{1-\emptyset}{1-\emptyset_2}\right)+n_j^{-1}log\left(\frac{\mathrm{pr}(H_0)}{\mathrm{pr}(H_2)}\right)}{log\left\{\frac{\emptyset_2(1-\emptyset)}{\emptyset(1-\emptyset_2)}\right\}}$$

- 만약 세 개의 point hypothesis 의 확률, 즉 prior 의 확률이 모두 1/3 으로 설정하면 ;

- $\lambda_{1j}, \lambda_{2j}$ 은 j(용량단계) 또는 n_j (현재 용량단계에 배정된 시험대상자 수)에 상관없이 임상시험에 걸쳐 동일한 상수가 됨
- 이 상수는 또한 LRT (likelihood ratio test) boundaries 임
- 용량설정을 위한 1상 임상시험 동안 용량단계에 상관없이 동일한 BOIN boundaries 를 사용할 수 있는 것은 실무적으로 매우 효율적
- 그러나 독성확률이 3개의 값 ($\emptyset_1, \emptyset, \emptyset_2$) 에서만 확률을 갖는다는 가정 (local BOIN의 가정, point mass distr.)의 적절성에 대한 의문

BOIN – How to set toxicity rate parameters?

- Question: $\emptyset_1, \emptyset, \emptyset_2$ 은 어떻게 결정하는가?

  $\emptyset_1, \emptyset_2$ 를 $\emptyset$ 와 너무 가깝게 설정하면 상대적으로 대상자수가 적은 1상 임상시험은 Target toxicity rate 으로 부터의 작은 차이를 구별해 낼 Power 가 부족함.

- 권장되는 수치: $\emptyset_1 \in [0.5\emptyset, 0.7\emptyset]$, $\emptyset_2 \in [1.3\emptyset, 1.5\emptyset]$

- BOIN default :

  $\emptyset_1 = 0.6\emptyset$, $\emptyset_2 \in 1.4\emptyset$

  i.e. Target toxicity rate 으로 부터 40% 차이,

  Target toxicity=0.25, $\emptyset_1$=0.15, $\emptyset_2$=0.35

Table 1. Values of λ_{1j} and λ_{2j} under the local BOIN design for various target toxicity rates with $\phi_1 = 0.6\phi$ and $\phi_2 = 1.4\phi$

Interval boundary	*Results for the following target toxicity rate ϕ:*					
	0.15	*0.2*	*0.25*	*0.3*	*0.35*	*0.4*
λ_{1j}	0.118	0.157	0.197	0.236	0.276	0.316
λ_{2j}	0.179	0.238	0.298	0.358	0.419	0.479

S. Liu and Y. Yuan (2015)

BOIN - Safety rule for overly toxic dose

- **기존(BOIN 이전)의 Interval design 의 단점 : 독성이 높은 용량에 시험대상자가 많이 배정되는 문제**

- Interval design 은 과거의 path 를 돌아보지 않고 오직 현재 용량단계에서의 Toxicity rate 의 추정치를 이용하여 다음단계를 결정함
- 따라서 만약 연속된 두 용량군 중 하나는 MTD 보다 훨씬 작고 다른 하나는 MTD 보다 훨씬 큰 경우, 이 두 용량단계를 bounce back and forth 할 수 있다.

- **Dose elimination rule** (beta-binomial model)

: 만약 $pr(p_j > \emptyset | \boldsymbol{n_j}, \boldsymbol{m_j}) > 0.95$ and $\boldsymbol{n_j} > \boldsymbol{3}$, 용량단계 j 와 그 이상의 용량단계들을 임상시험에서 제거한다. (첫 용량 단계이면 trial stop)

Table 1. Dose escalation/de-escalation rule for the BOIN design.

Actions*	The number of evaluable patients **at the current dose**														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Escalate if # of DLT ≤	0	0	**0**	0	0	**1**	1	1	**1**	1	2	**2**	2	2	**2**
De-escalate if # of DLT ≥	1	1	**1**	2	2	**2**	3	3	**3**	3	4	**4**	4	5	**5**
Eliminate if # of DLT ≥	NA	NA	**3**	3	3	**4**	4	4	**5**	5	6	**6**	6	7	**7**

용량증가
$\lambda_e \times \boldsymbol{n_j}$
0.197

$\lambda_d \times \boldsymbol{n_j}$
0.298
용량감소
용량제거

BOIN software 에 입력한 design parameter

- Target toxicity=0.25, $\emptyset_1$=0.15, $\emptyset_2$=0.35
- Number of doses =5
- Maximum sample size = 30
- Cohort Size = 3
- Stop if #patients in a dose level reaches = 15
- Using default elimination rule

BOIN - stop & estimate MTD

BOIN 의 dose transition 이 Stop 하는 경우

- 설정한 전체 Max Sample Size 에 도달한 경우
- 개별용량 코호트에 배정 가능한 Max Sample Size 에 도달한 경우
- BOIN 의 Safety Elimination Rule 에 의하여 가장 낮은 용량 코호트가 제거된 경우

BOIN 의 MTD 추정

- BION 의 dose transition 이 완료된 후 각 용량 코호트의 관측된 toxicity rate 을 이용하여 isotonic estimates 를 계산(pooled adjacent violators algorithm (Barlow et al. 1972))
- Monotonic 한 isotonic estimates 를 이용하여 설정한 target MTD(H_0) 와 가장 가까운 isotonic estimate 의 용량 단계를 MTD 로 선택

An example trial

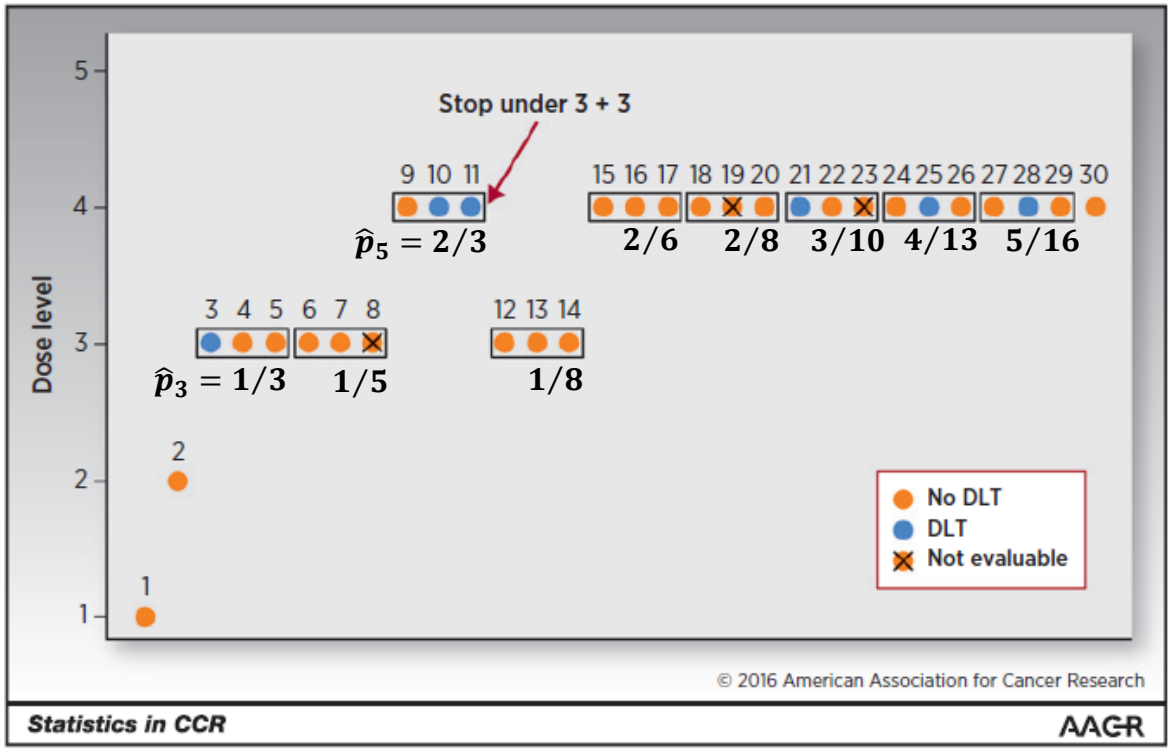


Table 1. Dose escalation/de-escalation rule for the BOIN design.

Actions*	The number of evaluable patients **at the current dose**																	
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Escalate if # of DLT ≤	0	0	**0**	0	1	**1**	1	1	**2**	2	2	**2**	3	3	**3**	3	4	**4**
De-escalate if # of DLT ≥	1	1	**2**	2	2	**3**	3	3	**4**	4	4	**5**	5	6	**6**	6	7	**7**
Eliminate if # of DLT ≥	NA	NA	**3**	3	4	**4**	5	5	**5**	6	6	**7**	7	8	**8**	8	9	**9**

최종적으로 용량단계 4에서 총 17명의 evaluable 대상자 중 5명의 DLT 가 발생하여

MTD = dose level 4, Estimated DLT rate = $5/17$ = 29.4%

BOIN software 에 입력한 design parameter

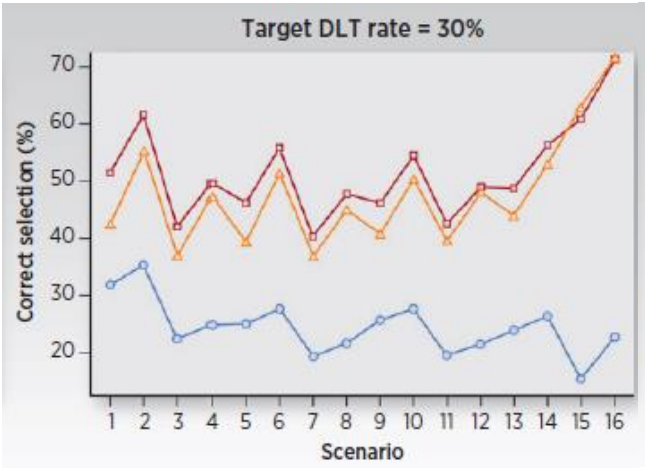
- Target toxicity=**0.3**, $\emptyset_1$=0.18, $\emptyset_2$=0.42
- Number of doses =5
- Maximum sample size = 30
- Cohort Size = 3
- Stop if #patients in a dose level reaches = 18
- Use default elimination rule
- Use accelerated titration : 첫 DLT 발생까지 cohort size=1

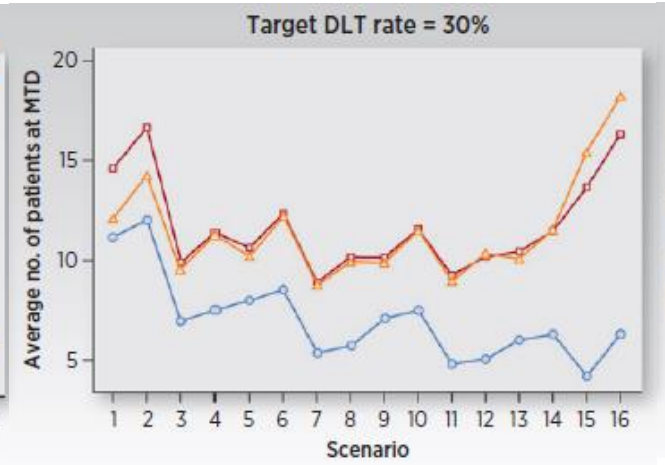
Simulation result (Yuan et al. 2016)

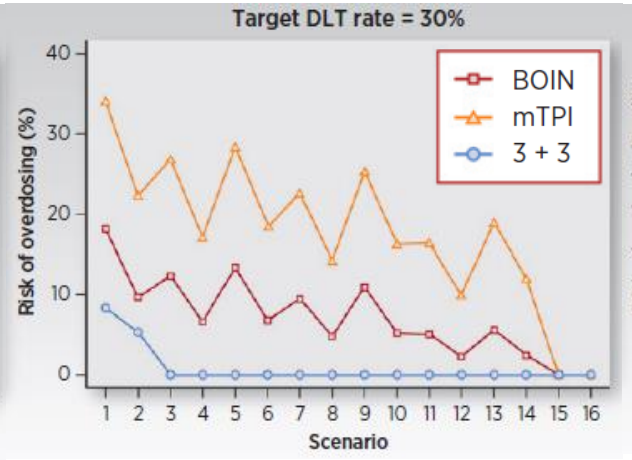
설정한 Target DLT rate (15%, 20%, 25%, 30%)과 16개의 다양한 toxicity scenario 를 설정하여 시뮬레이션 한 결과 아래의 4가지 기준에서 BOIN 이 3+3 과 mTPI 에 비하여 효율적이라고 주장 (Liu S. and Yuan Y. (2015) 에는 CRM 과의 비교결과 있음)

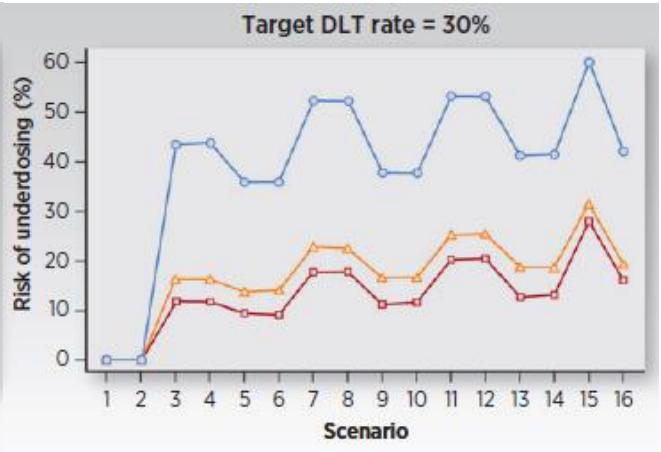
Performance metrics (10,000 번의 simulation)

1. 설정한 true MTD 를 선택한 비율
2. MTD 에 배정된 시험대상자의 수의 평균 (3+3 design 에서는 MTD 결정 후 BOIN 의 max SS 까지 MTD로 배정하는 방식으로 계산됨 -> 엄밀한 의미에서 1:1 비교는 불가)
3. Overdosing Risk : 60%/80% 이상의 환자들이 MTD 보다 높은 용량에 배정된 simulation 의 비율
4. Underdosing Risk : 60%/80% 이상의 환자들이 MTD 보다 낮은 용량에 배정된 simulation 의 비율









BOIN software in practice – design parameters

Bayesian Optimal Interval (BOIN) Phase I Design (PID-862): Version 1.0.9 *(New Input File)*

File Help

Design Parameters | Simulation Run | Estimate MTD

Doses

Number of Doses: 5

Starting Dose Level: 1

Sample Size

Maximum Sample Size: 30

Cohort Size: 3

Stop trial if # patients assigned to a single dose reaches this number and the decision is to stay: 18

☑ Use Accelerated Titration

Target Probability

Target Toxicity Probability: $\phi =$ 0.30

☐ Use the default alternatives to minimize decision errors (recommended)

Alternatives under which decision errors are minimized:

Underdosing: $\phi_1 =$ 0.18 Overdosing: $\phi_2 =$ 0.42

Safety

Eliminate dose j if it satisfies:

$$Pr(p_j > \phi | data) > p_E$$

☑ Use the default cutoff (recommended): $p_E =$ 0.95

☑ Uncheck this box to impose a more stringent safety stopping rule.

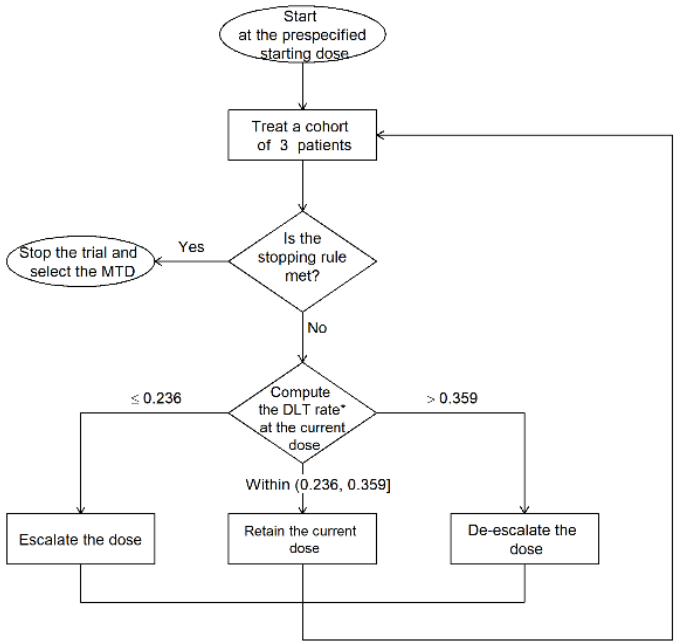
Show Escalation / De-escalation Table

Help

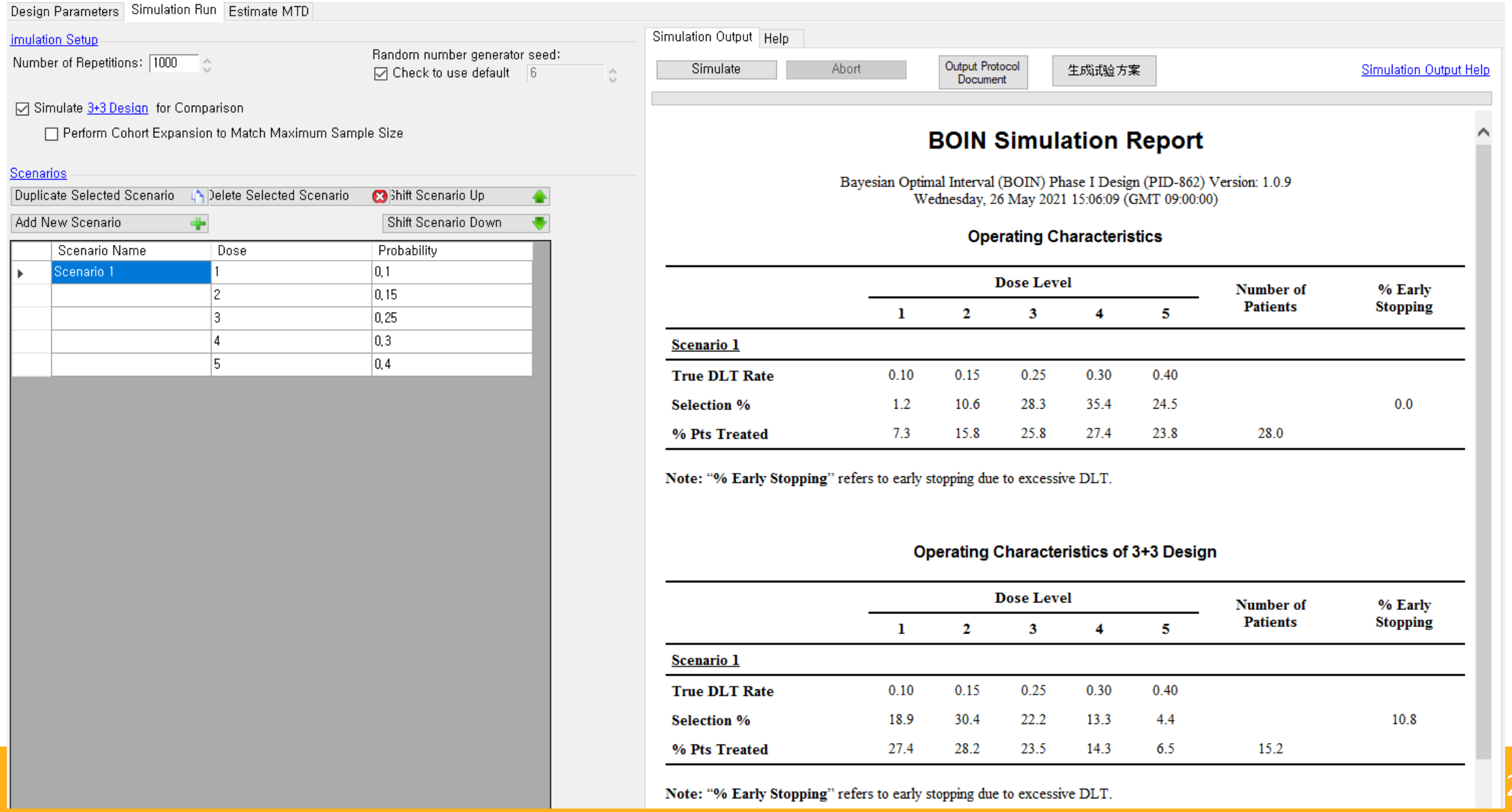
Table 1. Dose escalation/de-escalation rule for the BOIN design.

Actions*	The number of evaluable patients **at the current dose**																	
	1	2	**3**	4	5	**6**	7	8	**9**	10	11	**12**	13	14	**15**	16	17	**18**
Escalate if # of DLT ≤	0	0	**0**	0	1	**1**	1	1	**2**	2	2	**2**	3	3	**3**	3	4	**4**
De-escalate if # of DLT ≥	1	1	**2**	2	2	**3**	3	3	**4**	4	4	**5**	5	6	**6**	6	7	**7**
Eliminate if # of DLT ≥	NA	NA	**3**	3	4	**4**	5	5	**5**	6	6	**7**	7	8	**8**	8	9	**9**

* When none of the actions (i.e., escalate, de-escalate or eliminate) is triggered, stay at the current dose for treating the next cohort of patients. Note that "# of DLT" is the number of patients with at least 1 DLT, and "NA" means that a dose cannot be eliminated before treating 3 evaluable patients.



BOIN software in practice – simulation run



BOIN - output protocol document

NOTE: If you would like a **Microsoft Word** version of this protocol document template, simply select (hig
document, copy it, open a new Word document, and paste the protocol document template into the Word
Windows machines this can conveniently be accomplished by pressing **CTRL-A** to select (highlight) the
CTRL-C to copy it, and **CTRL-V** to paste it. Alternatively, opening the saved HTML file in Microsoft Word
results.

Template for Protocol Preparation
Trial Name:

We will employ the Bayesian optimal interval (BOIN) design (Liu and Yuan, 2015; Yuan et al., 2016) to fi
BOIN design is implemented in a simple way similar to the traditional 3+3 design, but is more flexible an
superior operating characteristics that are comparable to those of the more complex model-based desig
continual reassessment method (CRM) (Zhou, Yuan and Nie, 2018).

The target dose-limiting toxicity (DLT) rate for the MTD is $\phi = 0.25$ and the maximum sample size is 30. V
treat patients in cohorts of size 3. DLTs are defined in Section ###, and only those DLTs that occur within
be used for dose finding. As shown in Figure 1, the BOIN design uses the following rule, optimized to mi
probability of incorrect dose assignment, to guide dose escalation/de-escalation:

- if the observed DLT rate at the current dose is ≤ 0.197, escalate the dose to the next higher dose l
- if it is > 0.298, de-escalate the dose to the next lower dose level;
- otherwise, stay at the current dose.

For the purpose of overdose control, doses j and higher levels will be eliminated from further considerati
data) > 0.95 and at least 3 evaluable patients have been treated at dose level j, where p_j is the true DLT
$j = 1, \ldots, 5$. This posterior probability is evaluated based on the beta-binomial model $y_j \mid p_j \sim \text{binomial}(p_j)$
1), where y_j is the number of patients experienced DLT at dose level j. When the lowest dose is eliminate
safety. The probability cutoff 0.95 is chosen to be consistent with the common practice that when the targ
a dose with 2/3 patients experiencing DLT is eliminated. The above dose escalation/de-escalation and el
be equivalently presented in Table 1, which will be used to conduct the trial.

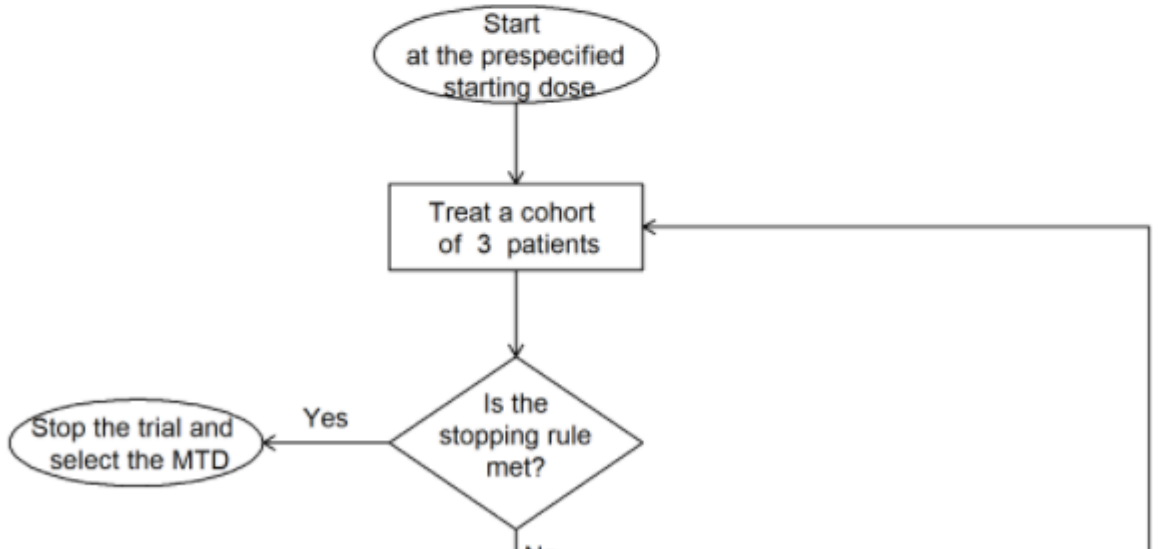
The steps to implement the BOIN design are described as follows:

1. Patients in the first cohort are treated at dose level 1.
2. To assign a dose to the next cohort of patients, conduct dose escalation/de-escalation according t
   in Table 1. When using Table 1, please note the following:
   a. "Eliminate" means eliminate the current and higher doses from the trial to prevent treating a
      these doses because they are overly toxic.
   b. When we eliminate a dose, automatically de-escalate the dose to the next lower level. Whe
      eliminated, stop the trial for safety. In this case, no dose should be selected as the MTD.
   c. If none of the actions (i.e., escalation, de-escalation or elimination) is triggered, treat the ne
      current dose.

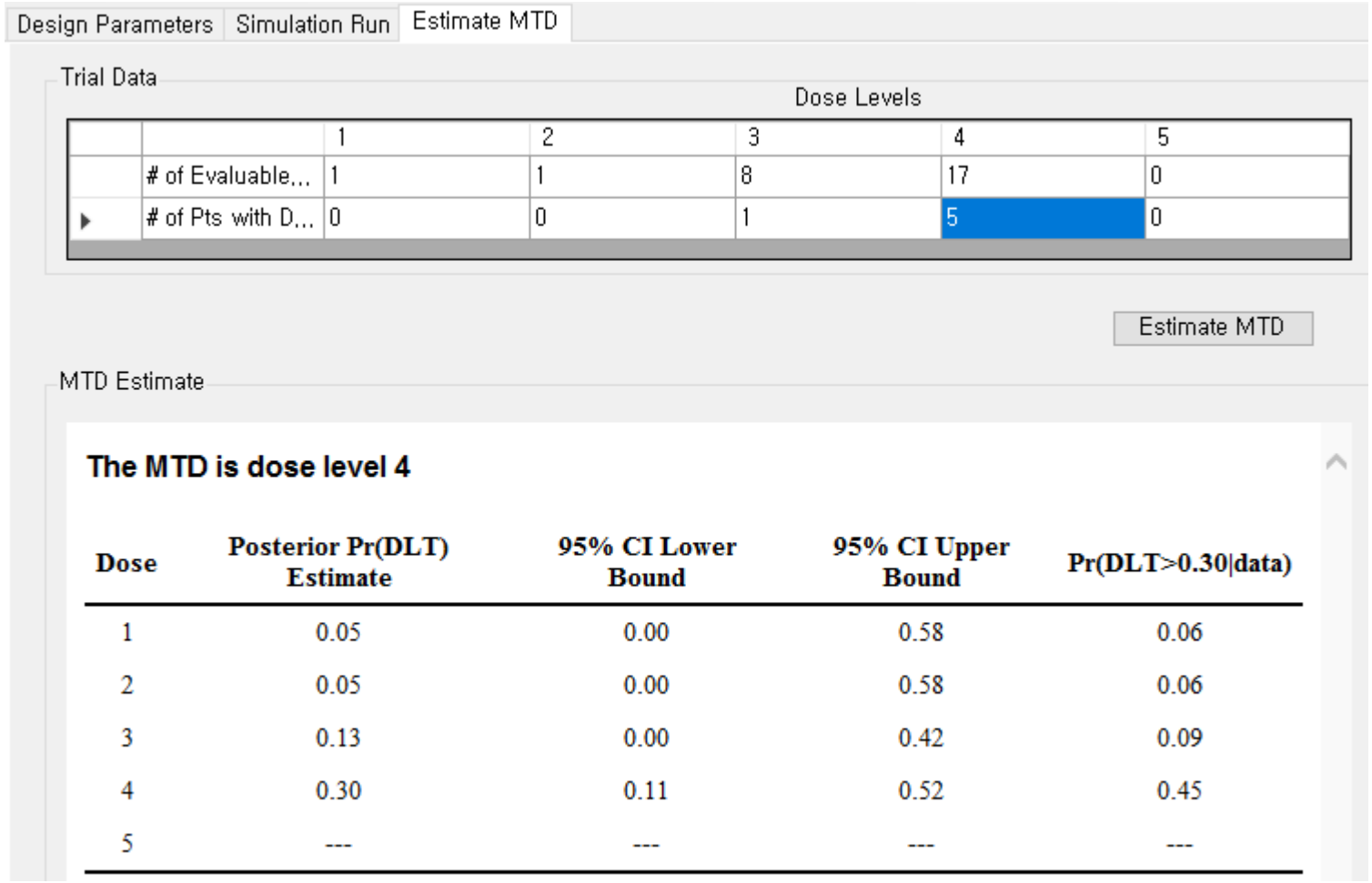
Table 1. Dose escalation/de-escalation rule for the BOIN design.

Actions*	The number of evaluable patients **at the current dose**											
	1	2	3	4	5	**6**	7	8	9	10	11	**12**
Escalate if # of DLT ≤	0	0	**0**	0	0	**1**	1	1	**1**	1	2	**2**
De-escalate if # of DLT ≥	1	1	**1**	2	2	**2**	3	3	**3**	3	4	**4**
Eliminate if # of DLT ≥	NA	NA	**3**	3	3	**4**	4	4	**5**	5	6	**6**

* When none of the actions (i.e., escalate, de-escalate or eliminate) is triggered, stay at the current dose for treating the next cohort of patients. Note that "# of DLT" is the number of patients with at least 1 DLT, and "NA" means that a dose cannot be eliminated before treating 3 evaluable patients.



BOIN software in practice – Estimate MTD



Dose	Posterior Pr(DLT) Estimate	95% CI Lower Bound	95% CI Upper Bound	Pr(DLT>0.30|data)
1	0.05	0.00	0.58	0.06
2	0.05	0.00	0.58	0.06
3	0.13	0.00	0.42	0.09
4	0.30	0.11	0.52	0.45
5	---	---	---	---

BOIN 의 장점

- 3+3 design 과 비교하여서는 현재 용량단계의 누적된 모든 정보를 사용하여 용량 증감을 결정하므로 효율적이다 – MTD 를 제대로 추정하고 되도록 많은 환자가 MTD 에 배정 되게 한다는 의미
- 3+3 design 에 비하여 자유롭게 설정 가능한 parameter 들이 많아 유연하다.
- Interval design 기반의 BOIN 은 복잡한 model based design 에 비하여 실제 임상시험 운용 시 적용하기 쉽고 간단하며, MTD 를 추정에 있어서 comparable 한 결과를 보이고 underdosing 이나 overdosing 을 할 Risk 가 낮다.
- Free Software 이용 가능하며 프로토콜 Templet 이 생성된다.

References

- **BOIN software - desktop version v1.0.9**

  https://biostatistics.mdanderson.org/SoftwareDownload/SingleSoftware/Index/99

- **BOIN cloud software v2.6.0**

  https://www.trialdesign.org/

- **Single Drug Study:**
  [1] Liu S. and Yuan Y. (2015) Bayesian Optimal Interval Designs for Phase I Clinical Trials, *Journal of the Royal Statistical Society: Series C*, 64, 507-523.
  [2] Yuan Y., Hess K.R., Hilsenbeck S.G. and Gilbert M.R. (2016) Bayesian Optimal Interval Design: A Simple and Well-performing Design for Phase I Oncology Trials, *Clinical Cancer Research*, 22(17), 4291-4301.
  [3] Yuan Y., Lin R., Li D., Nie L. and Warren K.E. (2018) Time-to-event Bayesian Optimal Interval Design to Accelerate Phase I Trials, *Clinical Cancer Research*, 24, 4921-4930.

- **Combination Drug Study Seeking a Single MTD:**
  [4] Lin R. and Yin G. (2017) Bayesian Optimal Interval Design for Dose Finding in Drug-combination Trials, *Statistical Methods in Medical Research*, 26, 2155-2167.

- **Combination Drug Study Seeking an MTD Contour:**
  [5] Zhang L. and Yuan Y. (2016) A practical Bayesian design to identify the maximum tolerated dose contour for drug combination trials, *Statistics in Medicine*, 35, 4924-4936.

- **Comparison of BOIN to Other Designs:**
  [6] Zhou H., Murray T., Pan H. and Yuan Y. (2018) Comparative review of novel model-assisted designs for phase I clinical trials, *Statistics in Medicine*, 37, 2208-2222.
  [7] Zhou H., Yuan Y. and Nie L. (2018) Accuracy, safety, and reliability of novel phase I trial designs, *Clinical Cancer Research*, 24(18), 4357-4364.