THE USE OF NOVEL PHASE I ADAPTIVE BAYESIAN DESIGNS IN RARE DISEASES

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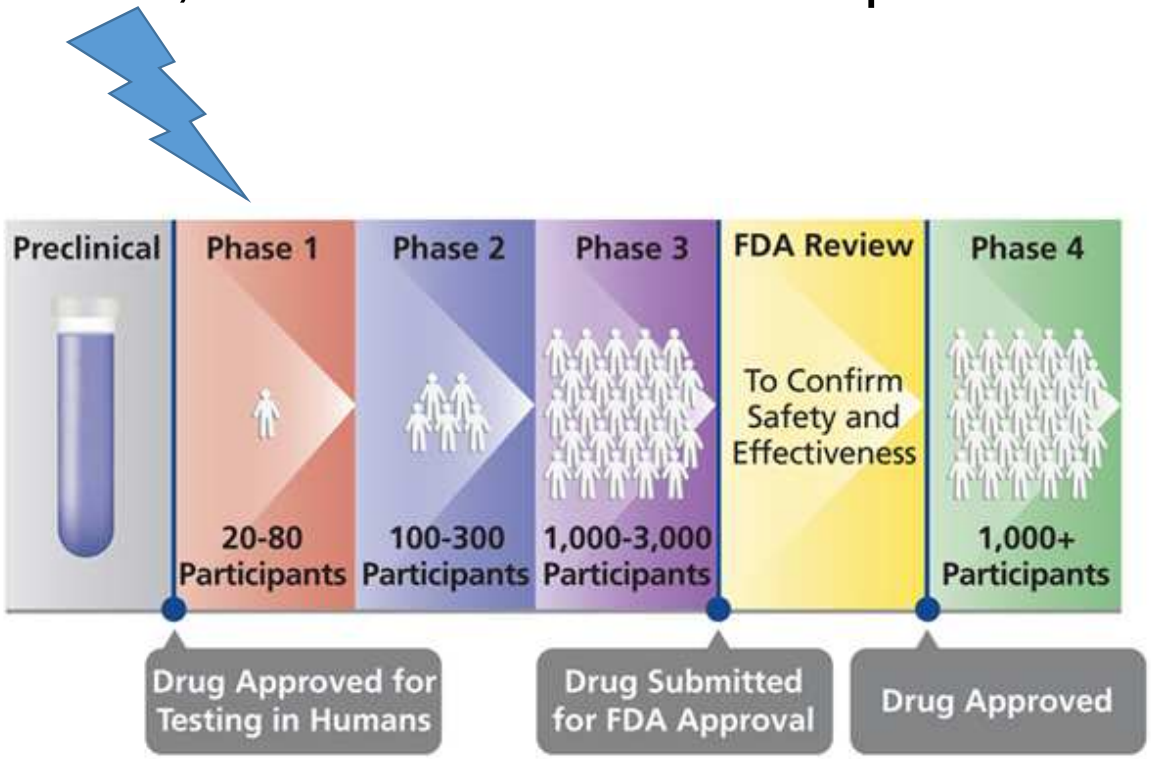
Outline

1. Phase I trials
2. Interval based designs
3. Proposals: an amendment to the designs and a new graphical tool
4. Simulation study in a rare disease setting
5. Motivating clinical trial
6. Conclusions

Phase I trials - Background

- ✓ First in men studies
- ✓ Few patients
- ✓ Single arm, non randomized and open label



Phase I trials - Background

The goal of phase I trials is to find the maximum tolerated dose (MTD) with a target toxicity rate.

Challenges:

- ✓ Estimate MTD accurately and precisely
- ✓ Use all available data efficiently
- ✓ Minimize the number of patients exposed to severe toxicity or to sub-therapeutic doses

Phase I trials: Background

A lot of approaches have been proposed using toxicity (Dose Limiting Toxicity=DLT) as primary **binary endpoint**.

Class	Design
Rule-based	1989 - 3+3 (Storer) 1997 - Accelerated titration (Simon) ….
Model-based	1990 - Continual Reassessment Method (CRM) (O'Quigley) 1998 - Escalation With Overdose Control (EWOC) (Babb) 2008 - Bayesian Logistic EWOC (Neuenschwander) ….

Phase I trials: Background

Model-based designs are superior to rule-based designs in identifying MTD.

Challenges in set-up and implement remain and have limited their widespread use.

Period	Published trials using CRM	Source
1991-2006	1.6 %	Rogatko (2007)
2007-2016	6.4%	van Brummelen (2016)

Motivating clinical context in a rare disease

CANDIDATE DESIGNS:

3+3 design

CRM

Interval based designs

- ✓ **mTPI** (Ji&Yang, 2010) and **BOIN** (Liu&Yuan, 2015), with further extensions (2017) **mTPI2** (Guo) and **Keyboard** (Yan)
- ✓ offer an alternative to CRM
- ✓ better performance than rule based designs and simple to implement (Yuan, 2016)
- ✓ previous comparison studies with CRM only for n≥24 patients (Horton, 2017; Zhou 2018)

Interval Based Designs (IBD)

Let:

- $d_1 < \ldots < d_i < \ldots < d_K$ $(i=1 \ldots K)$, the sequence of K fixed doses
- p_T = the target toxicity probability
- p_i = Pr(toxicity) at dose i $(i=1,\ldots K)$
- x_i = # of subjects treated at dose i experiencing toxicity $(i=1,\ldots K)$
- n_i = # of subjects treated at dose i $(i=1,\ldots K)$ – cohort of size 3 is not required

Assume that:

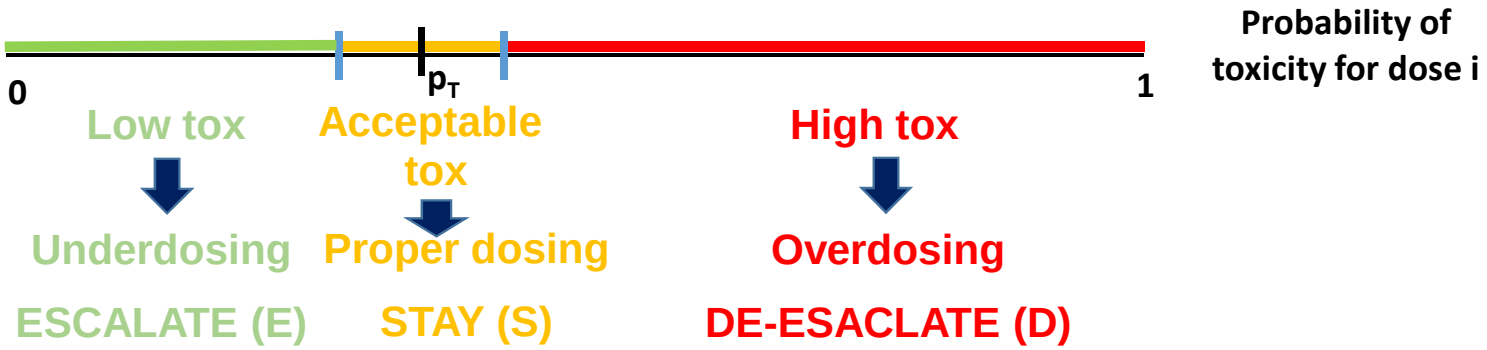
- Distribution of x_i is Bin(n_i, p_i)
- Priors of p_i are beta(α,β), usually with $\alpha = \beta = 1$
- Posteriors of p_i are beta($x_i + \alpha$, $n_i - x_i + \beta$)
- Monotonicity $p_1 < p_2 < \ldots < p_K$

IBD: hallmark

If patients are treated at dose d_i, there are 3 possible actions:

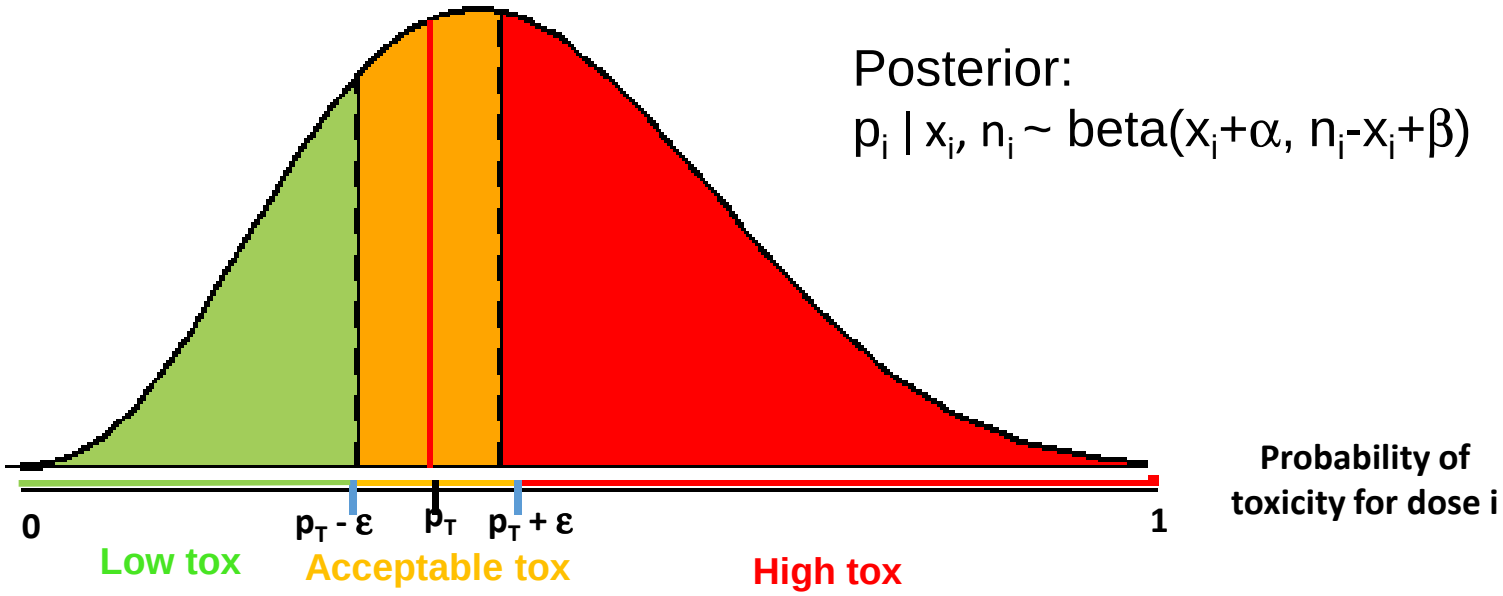
1. **Escalate (E)** to dose i+1
2. **Stay (S)** at dose i
3. **De-escalate (D)** to dose i-1

Partition of the [0,1] p_i axis in three sub-intervals that are associated with different decisions:



Decision rule: depends on the specific design

mTPI design: dose assignement

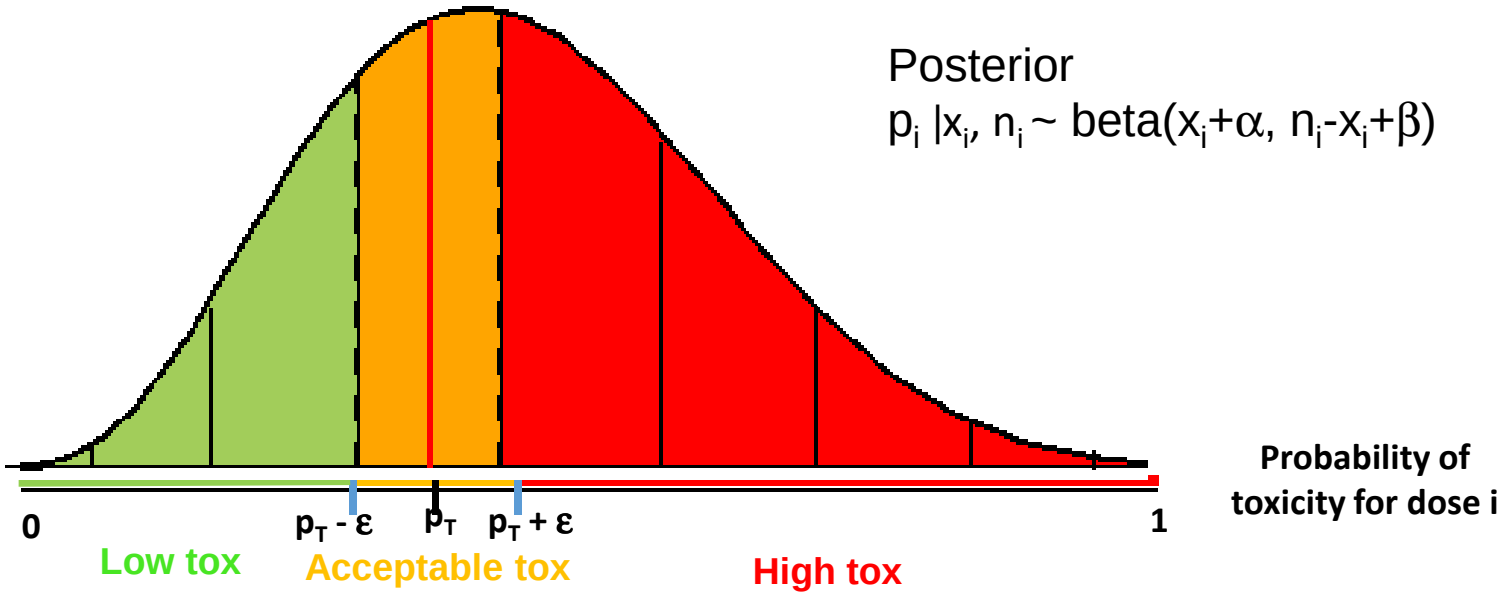


Calculate the Uniform Probability Mass (UPM):

UPM(interval)=posterior Pr(interval) / lenght(interval)

Choose E, D or S depending on which interval has highest posterior mass.

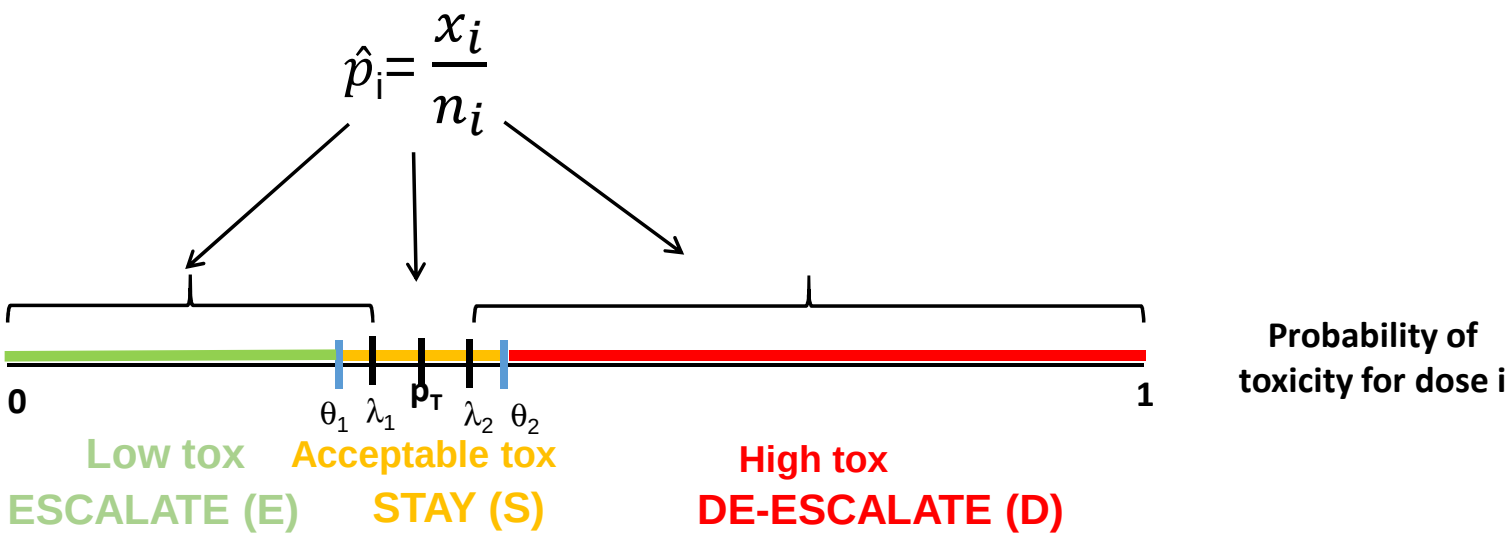
Keyboard & mTPI2 design: dose assignement



Calculate the posterior probability of toxicity in each interval

Choose E, D or S depending on which interval has highest probability

BOIN design: dose assignement



Determine the optimal sub-interval around p_T defined by λ_1 and λ_2 in the EI

Estimate the observed toxicity rate of the current dose d_i

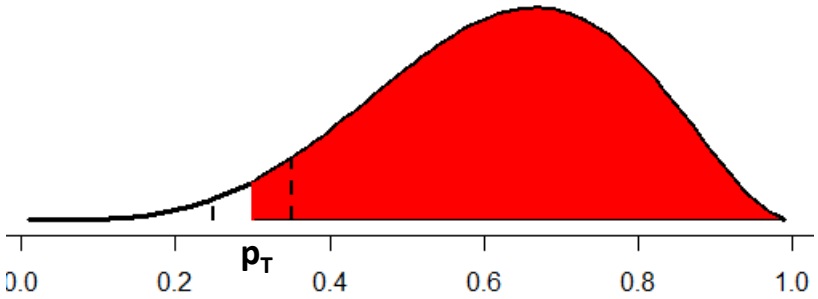
Choose E, D or S depending on the position of $\hat{p}_i$

IBD: stopping rules and trial termination

Stopping rules for safety:

1) Early study termination: $Pr(p_1 > p_T \mid x_i, n_i) > 0.95$

2) Dose exclusion: $Pr(p_i > p_T \mid x_i, n_i) > 0.95$



Trial Termination when the maximum sample size is reached.

IBD: Trial Monitoring Table

Trial Monitoring Table: decisions rules for each dose

Cumulative number of pts treated at dose i

Number of DLT

	3	6	9	…
0	E	E	E	
1	S	E	E	
2	D	S	E	
3	DU	D	S	
4		DU	D	
5		DU	DU	
6		DU	DU	
7			DU	
8			DU	
9			DU	
…				

E=Escalate
S=Stay
D=de-escalate;
DU=De-escalate and exclude dose (safety rule)

IBD: MTD selection

At the end of the trial, **all observed data** are used for MTD selection.

MTD is the dose, between the admissible doses satisfying the safety criterion (i.e. $Pr(p_i > p_T \mid \text{data}) < 0.95$), with the isotonic estimates of toxicity rate ($\hat{p}_i^*$) closest to the target p_T .

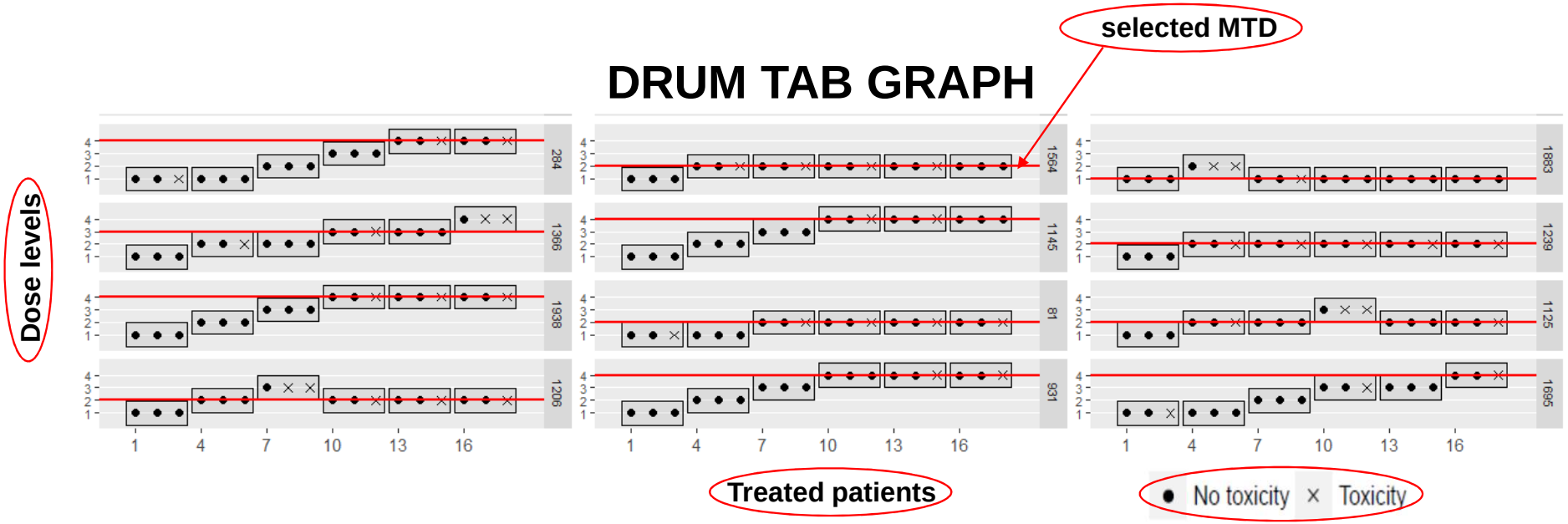
$$\min_i |\hat{p}_i^* - p_T|$$

N.B. Isotonic transformation are obtained applying the Pooled Adjacent Violators Algorithm (PAVA, Barlow et al. 1972) and assure that:

$$\hat{p}_1^* \leq \cdots \leq \hat{p}_i^* \leq \cdots \leq \hat{p}_K^*$$

IBD: patterns and graph

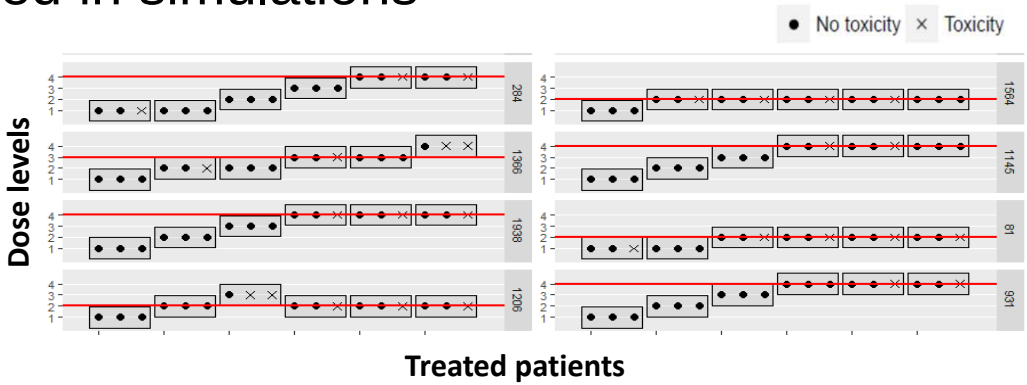
All the toxicity configurations occurring in a trial can be explored.



IBD: patterns and graph

Drum tab graphs can display:

1) **all the patterns**,
2) the **most likely patterns** observed in simulations
3) **conditional patterns**



Drum tab graphs are useful:

1) <u>at the design stage to:</u>
   - ✓ facilitate communication and understanding
   - ✓ help in fine-tuning designs parameters
2) <u>at the trial conduct stage to:</u>
   - ✓ supervise the future

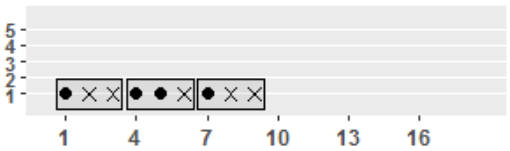
IBD: a revised version (1)

We introduced two amendments to the original designs

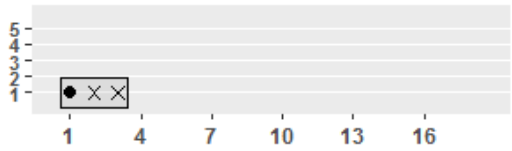
1) Early trial termination at the lowest dose

ξ=95%

Original design



Revised design - R



Cumulative number of pts treated at dose1

Number of DLSt

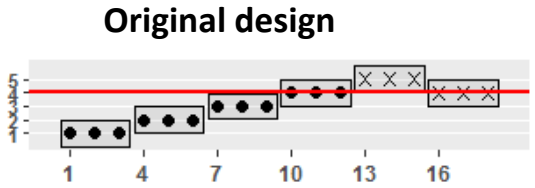
	3	6	9	…
0	E	E	E	
1	S	E	E	
2	D	S	E	
3	DU	D	S	
4		DU	D	
5		DU	DU	
6		DU	DU	
…				

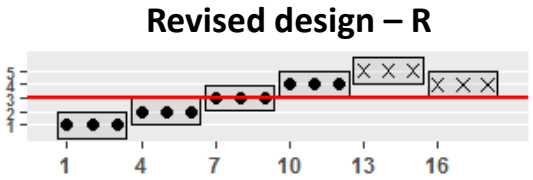
E=Escalate
S=Stay
D=de-escalate;
DU=De-escalate and exclude dose (safety rule)

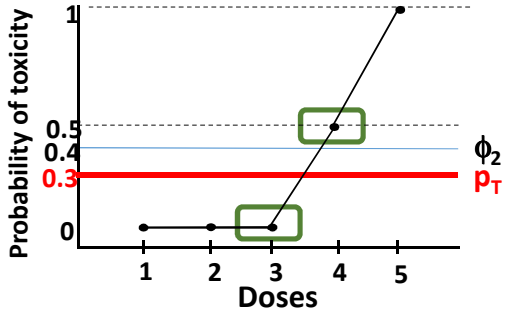
IBD: a revised version (2)

2) MTD selection

p_T=30%
θ_2=40%
ξ=95%







Admissible doses: $\Pr(p_i > 0.3 \mid x_i, n_i) < 0.95$

For i=4: $\Pr(p_4 > 0.3 \mid x_4=3, n_4=6) = 0.87$

MTD definition:

Dose with the (isotonic) estimates of toxicity rate closest to the target p_T, **but not superior to the upper boundery of the interval of acceptable toxicity.**

Simulation study: protocol

SIMULATION PARAMETERS

Dose levels: K= 4, 5
Scenarios of toxicity: 18 (5 doses), 14 (4 doses)
Sample size: n= 15, 18, 21
Cohorts size: 1, 3 patients
Simulations: 2000

DESIGN PARAMETERS

Toxicity target: p_T=0.3 (0.25, 0.20)
Overdose control: ξ= 0.90, 0.95
mTPI: $\varepsilon_1 = \varepsilon_2$=0.05
BOIN: λ_1=0.25; λ_2=0.35
CRM: δ=0.05

Based on the design parameters we considered:
BOIN=mTPI2=Keyboard

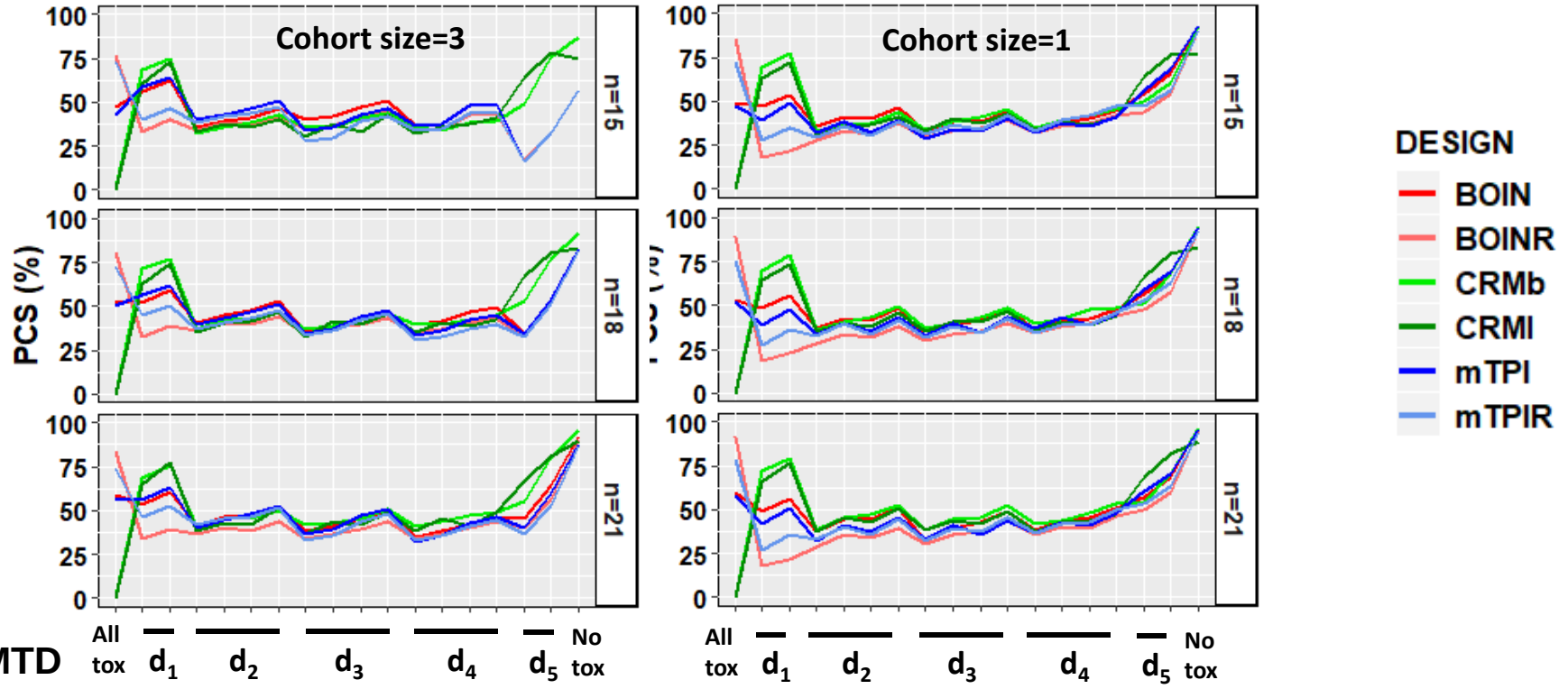
Six designs were compared:
2 BOIN (original, revised)
2 mTPI (original, revised)
2 CRM (Bayesian, Likelihood)

Available R script for mTPI, packages BOIN and dfcrm for BOIN and CRM, respectively

Simulation study: results

(5 doses, $p_T = 0.3$ and $\xi = 0.95$)

MTD selection: probability of correct selection (PCS)

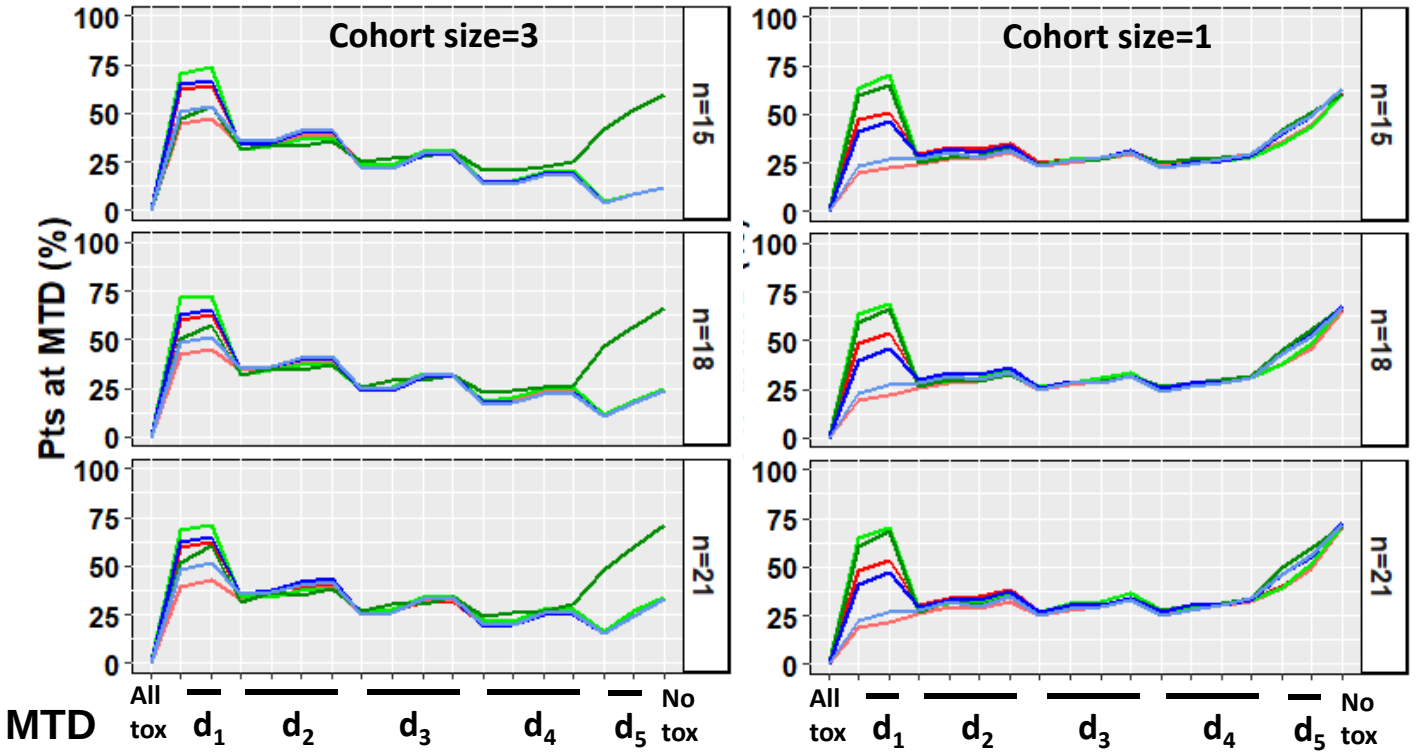


- CRM = IBD in general (no difference with ↑n, when MTD is in dose 5 and cohort of 3)
- CRM < IBD if all doses are toxic (revised IBD better)
- CRM > IBD if MTD is at first dose

Simulation study: results

(5 doses, $p_T = 0.3$ and $\xi = 0.95$)

Patient allocation: average % of patients allocated to MTD

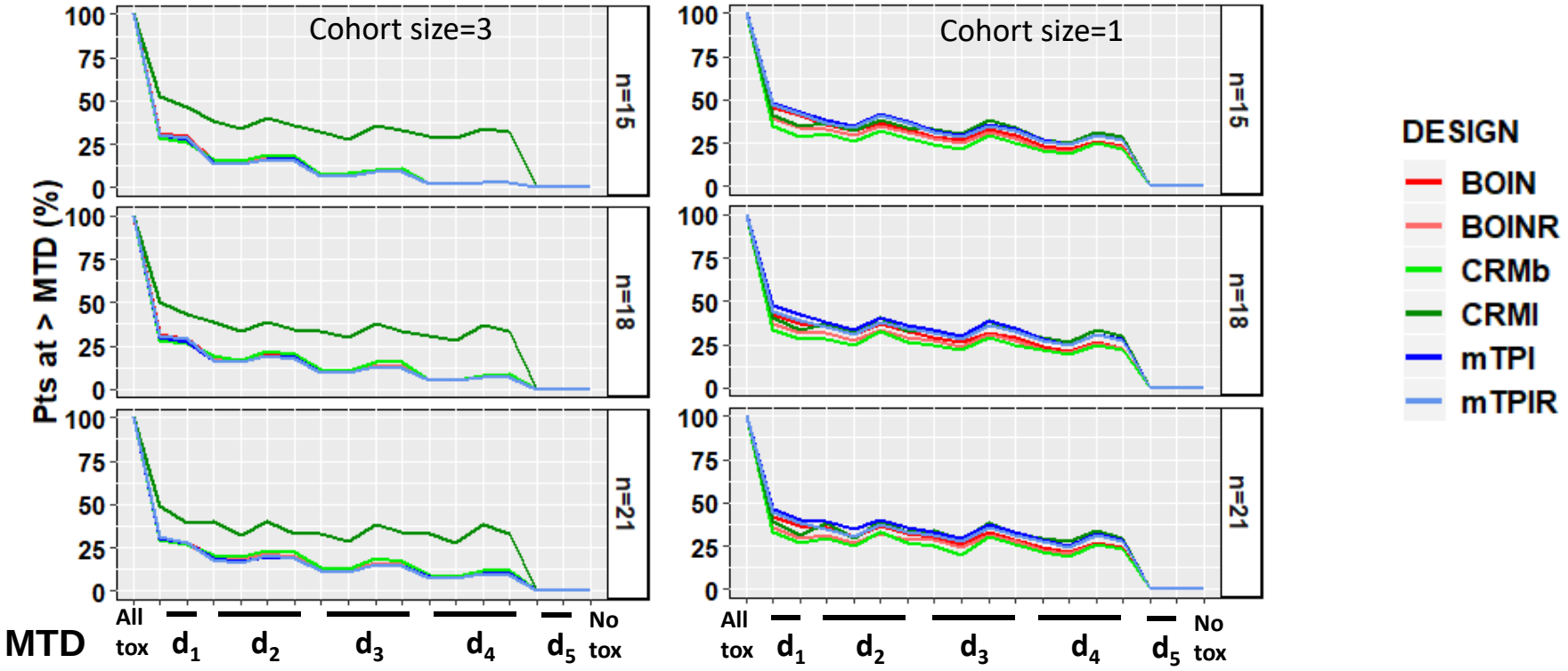


- CRM = IBD in general
- Lik CRM > IBD when MTD is in dose 5

Simulation study: results

(5 doses, $p_T = 0.3$ and $\xi = 0.95$)

Overdose control: average % of patients allocated to a dose above the MTD

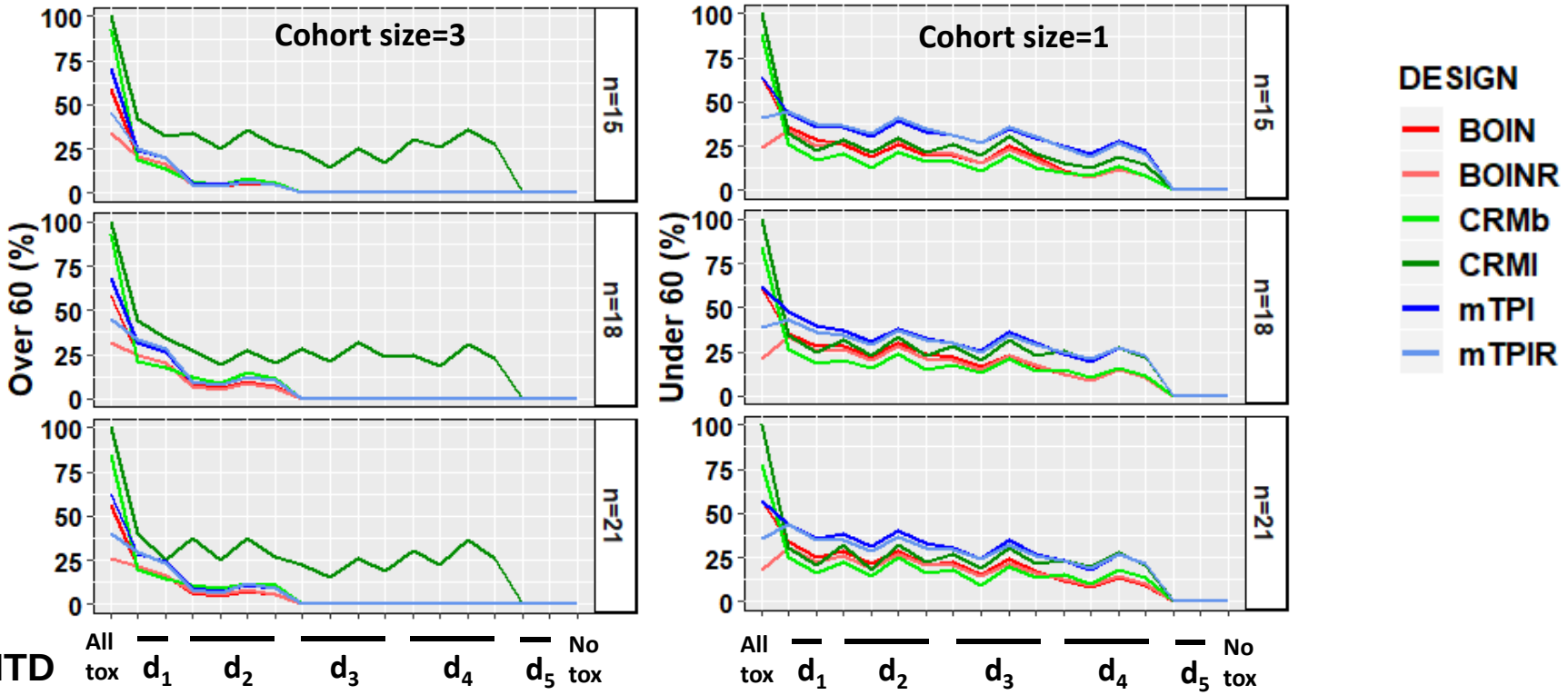


- CRM = IBD in general
- CRM < IBD when MTD is in dose 1

Simulation study: results

(5 doses, $p_T = 0.3$ and $\xi = 0.95$)

Risk of overdosing: % of trials in which the proportion of patients assigned to doses higher than the target toxicity pT reaches at least 60%



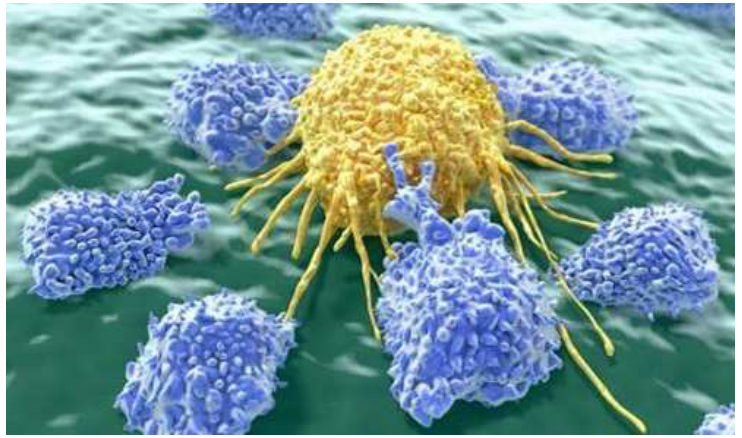
- Lik CRM < IBD when cohort size is 3
- Lik CRM ≈ mTPI < BOIN & Bay CRM when cohort size is 1

Motivating clinical context

Clinical question: safety of donor derived Cytokine Induced Killer (CIK) cells transduced with a transposon CD19 Chimeric Antigen Receptor gene (CARCIK-CD19)

Patient population: adult and pediatric patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL), after Hematopoietic Stem Cell Transplantation (HSCT).

Design: single arm, multi-center, phase I



Motivating clinical context

Dose levels: 4 doses

Sample size: 18 patients treated in cohorts of 3

Dose Limiting Toxicity: any life-threatening (grade 4) Cytokine Release Syndrome (CRS)

Enrollment: patients will be enrolled in a staggered manner (waiting two weeks prior to treating the next patient) for the purpose of assessing the acute safety profile.

Trial Monitoring: a DSMC and Italian Health Authorities will supervise the trial.

BOIN design:

- ✓ **Target toxicity rate:** 30%
- ✓ **Tolerance toxicity interval:** 20-40%
- ✓ **Optimal boundaries of toxicity probability:** 24.5% - 34.5%
- ✓ **Safety rules:**

$\Pr(p_1 > 30\% \mid \text{current data}) > 0.90$

$\Pr(p_i > 30\% \mid \text{current data}) > 0.90 \ \forall \ i=2,3,4$

Trial Monitoring Table

Number of DLTs	Cumulative number of patients treated at each dose					
	3	6	9	12	15	18
0	E	E	E	E	E	E
1	S	E	E	E	E	E
2	DU	S	E	E	E	E
3	DU	D	S	S	E	E
4		DU	D	S	S	S
5		DU	DU	D	S	S
6		DU	DU	DU	D	S
7			DU	DU	DU	D
8			DU	DU	DU	DU
9			DU	DU	DU	DU
10				DU	DU	DU
11				DU	DU	DU
12				DU	DU	DU
13					DU	DU
14					DU	DU
15					DU	DU
16						DU
17						DU
18						DU

E=Escalate **S**=Stay **D**=de-escalate;
DU=De-escalate and never use again (safety rule)

Conclusions

1. Interval based designs are a valid alternative to CRM in phase I trials, **even in rare diseases**.

2. BOIN-R design slightly better than the original and revised versions of mTPI.

3. The operating characteristics do not tell you everything.
   For interval based designs, we recommend to assess also:
   i) trial monitoring tables
   ii) patterns (especially in rare diseases)

4. We propose the “Drum tabs graphs” for pattern representation. They are useful:
   i) for the calibration of design parameters,
   ii) as an auxiliary tool in simulations,
   iii) as an effective instrument to communicate with clinicians/authorities.

Aknowledgments

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THANK YOU
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