Intro to Bayesian Adaptive Phase I Trials

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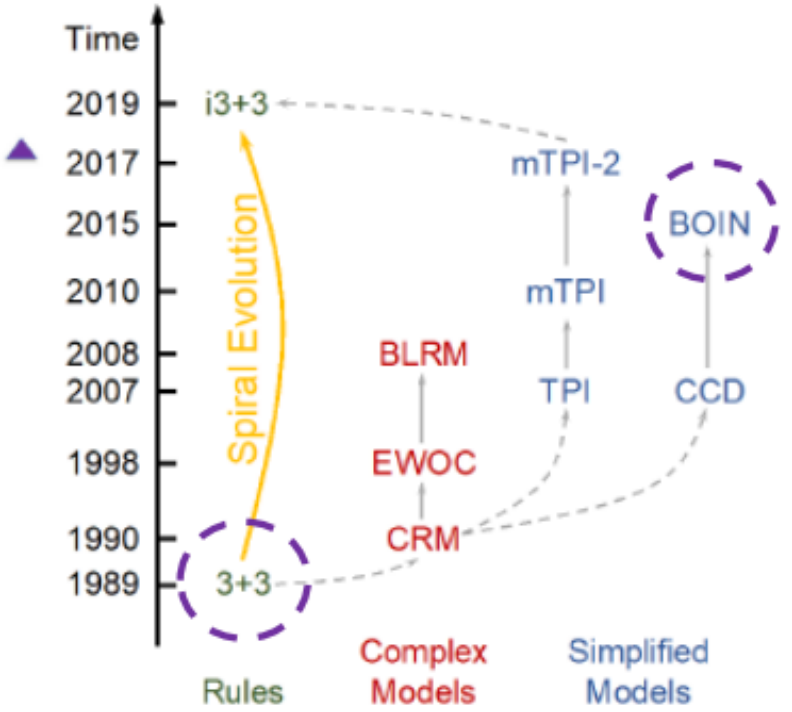
Early Phase Dose-finding Designs

- Algorithm-based designs: Simple, prespecified rules, inefficient MTD finding. e.g., 3+3 and its variants
- Model-based designs: better performance than 3+3, but statistically and computationally complex.
  - CRM(continual reassessment method) -1990
- Model-assisted designs: Simplicity of algorithm-based designs + performance of model-based designs.
  - BOIN: Bayesian optimal interval (BOIN) design.

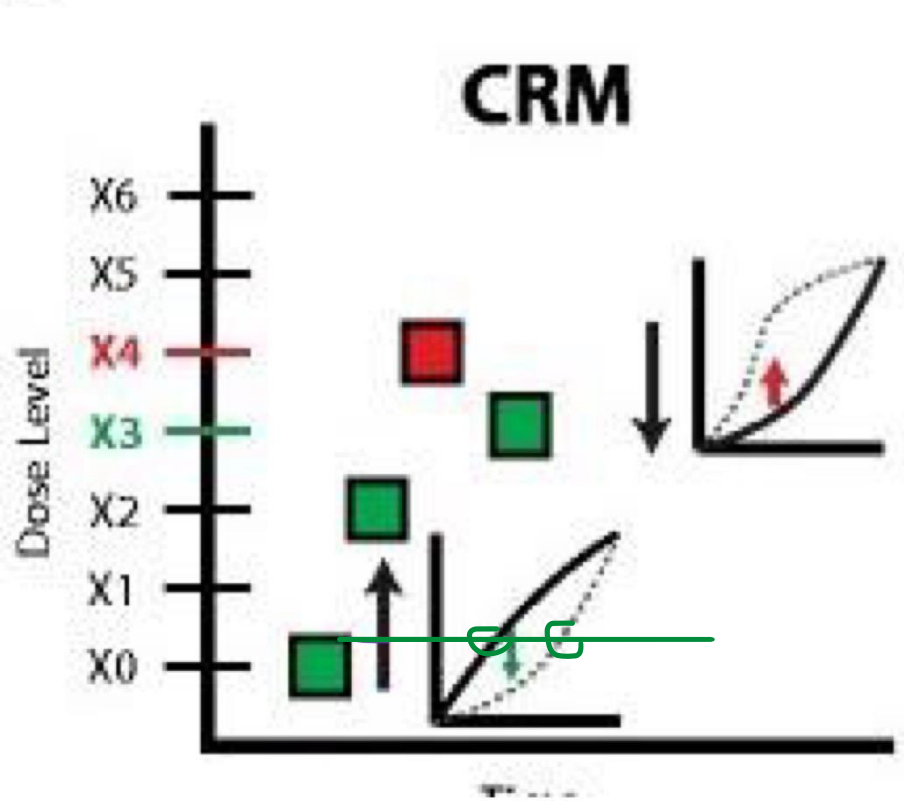


Adapted from Yiwen, DFCI, 2019

Continual reassessment method (CRM)

How it works?

- Initial dose-toxicity curve specified(skeleton) → the guess of the dose-toxicity relationship.
- Dose-toxicity curve updated after patient(s) toxicity data.
- Next dose level picked based on updated dose-toxicity curve.
- MTD is determined by all the information collected and provide a confidence interval.



Adapted from Fangxin, DFCI, 2020

CRM Key Components

- **Dose-toxicity skeleton:** The set of expected DLT probabilities at the dose levels of interest and is specified by one or more clinician before the trial.
- **Dose-toxicity model:** Model the relationship between dose and the risk of observing a DLT. It describe the probability of a patient experiencing a DLT at a given dose.

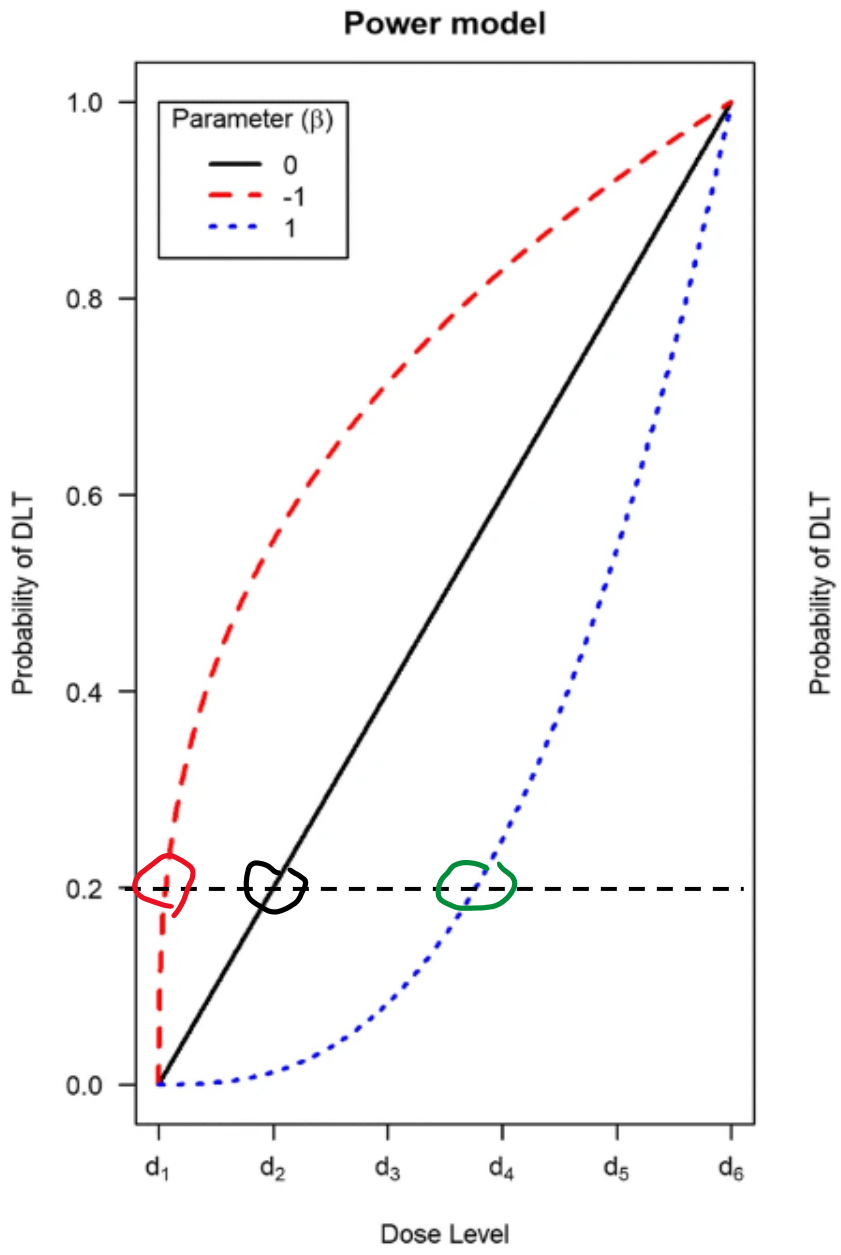
$$p(\beta, d) = d^{\{\exp(\beta)\}}$$

p: the true DLT probability
d: dose label
β : unknown parameter, with a prior distribution

→ it links the true dose-toxicity curve with prior estimate.

- **Safety stopping rule**: The estimated probability of all dose levels having a DLT rate above the target rate (ϕ) is at least 95%.

$$\Pr(p_1 > \Phi | data) > 0.95$$



Common Choices of Dose-Toxicity Model

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	$\frac{exp(\beta_1 + exp\ (\beta_2)\ d)}{1 + exp(\beta_1 + exp\ (\beta_2)\ d)}$	$\frac{\ln(\frac{p_i}{1-p_i}) - \beta_1}{exp(\beta_2)}$	$\beta_1 = 0, \beta_2 = 0$	$\ln(\frac{p_i}{1-p_i})$

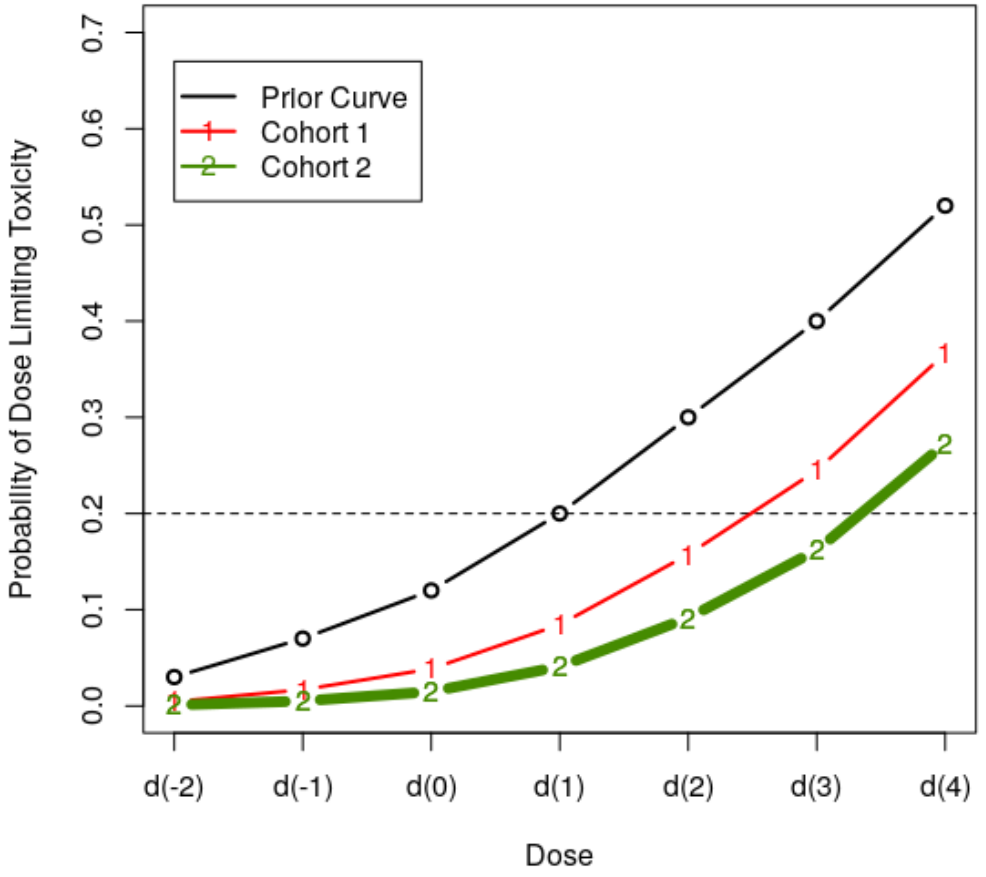
Notation: p_i = skeleton probability of DLT at i^{th} dose level; d_i = dose label for for i^{th} dose level

How's the next dose level picked?

- After each patient cohort is treated, CRM updated the estimate of the dose-toxicity curve based on the accumulating DLT data across all dose levels.
- To Assign the next cohort of patients to the "optimal" dose-whose posterior estimate of the true DLT probability is closes to the target ϕ

  If DLT(s) => lift the dose-toxicity curve => dose-escalation

  If no DLT(s) tends => lower the dose-toxicity curve => dose escalation



Running the trial

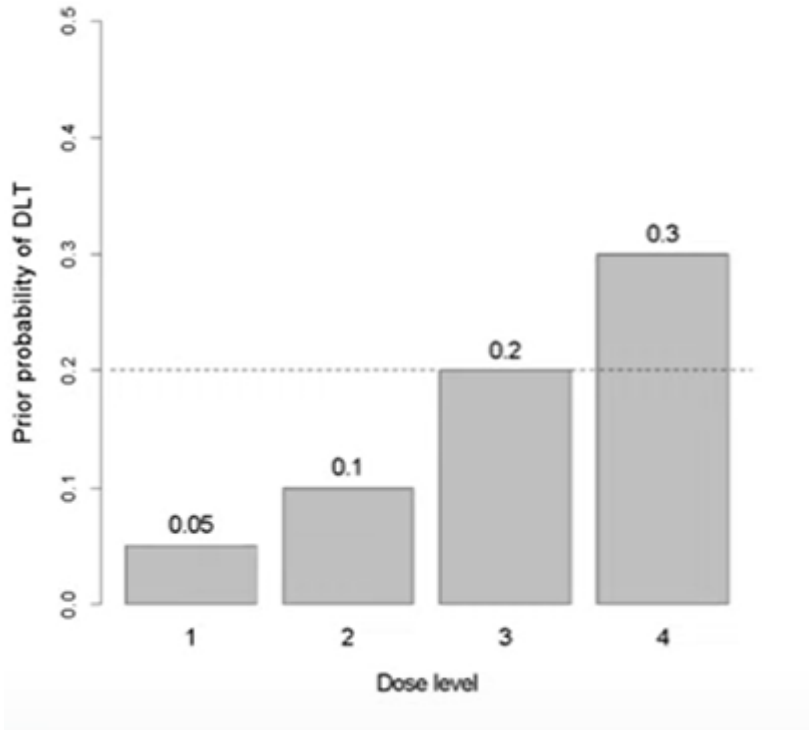
1. Enroll cohort of patients on current dose and observe DLTs
2. Calculate posterior distribution of beta and E(β) based on prior distribution and observed DLT information to date
3. Use E(β) to update dose-toxicity curve
4. Assign next cohort of patients to dose level with posterior probability closest to target toxicity rate
5. Typical escalation rules:
    a. Does escalation may not skip dose levels
    b. Dose de-escalation may skip dose levels
6. Trail ends after target sample size is accrued or stopping rule reached.
    Please be aware of there is no power calculation, the sample size is based on the level of precision, finance and timeline consideration.
7. MTD is identified as dose level with final posterior probability of DLT closest to target toxicity rate.

(Goodman et al, stat med. 1995; 14:1149-61)

CRM example

- DLT threshold = 20%
- Enroll patients sequentially (cohort size: n = 1)
- Star with the lowest dose level.
- Dose escalation:
  - Only increase 1 dose at a time
  - Escalate to dose with posterior probability closest to threshold
- Dose de-escalation: may skip doses
- Stop at N = 18 patients

Dose level	# Patients	# DLTs
1 - Start	0	0
2	0	0
3	0	0
4	0	0

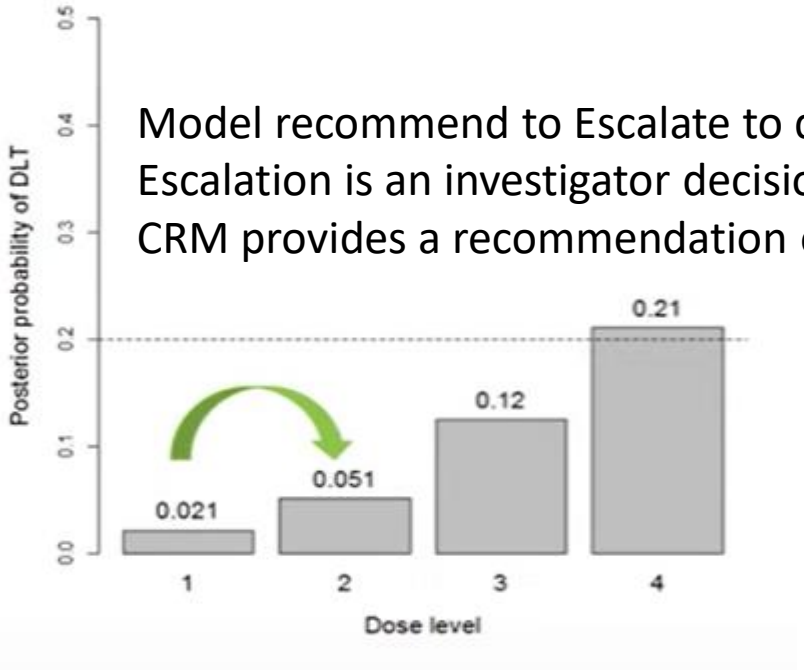


Adapted from Windy, London, 2022

Patient # 1 no DLT

Dose level	# Patients	# DLTs
1	1	0
2	0	0
3	0	0
4	0	0

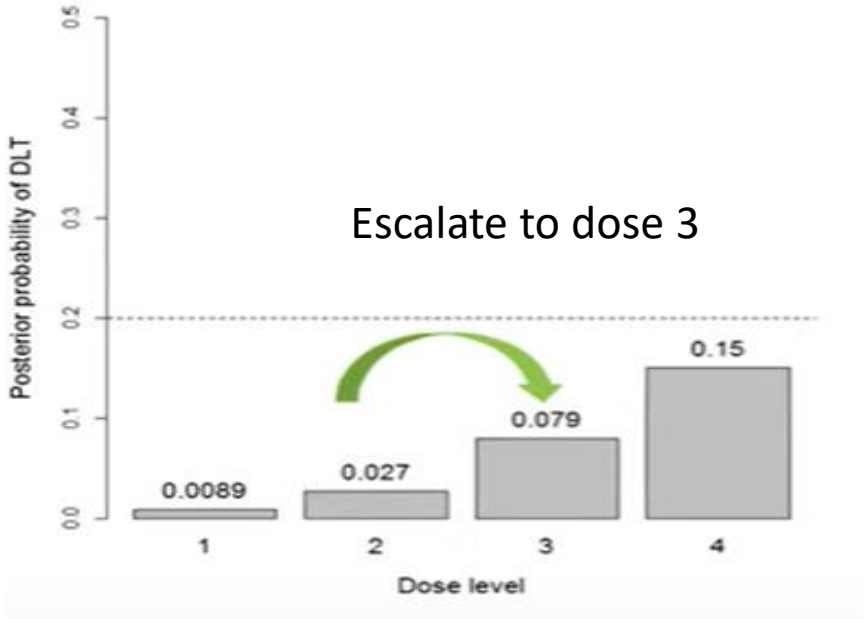
Model recommend to Escalate to dose 2
Escalation is an investigator decision.
CRM provides a recommendation only.



Patient # 2 no DLT

Dose level	# Patients	# DLTs
1	1	0
2	1	0
3	0	0
4	0	0

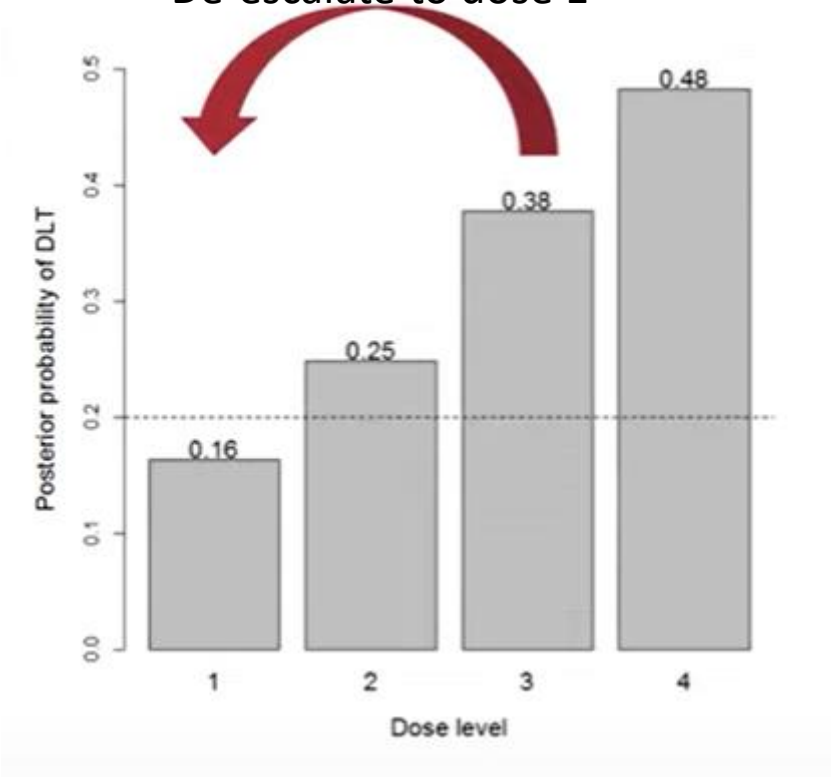
Escalate to dose 3



Patient #3 DLT

Dose level	# Patients	# DLTs
1	1	0
2	1	0
3	1	1
4	0	0

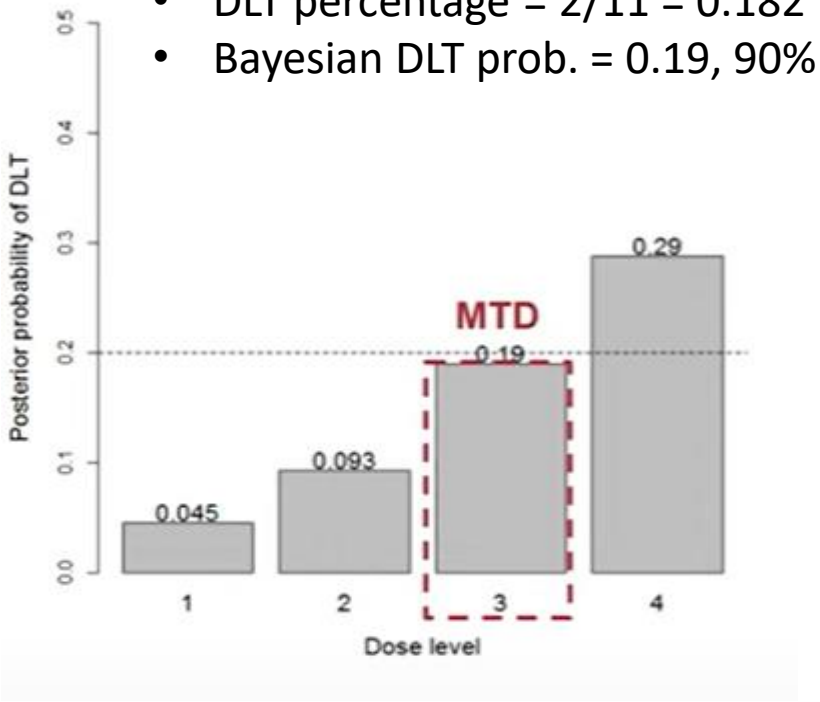
De-escalate to dose 1



Study complete at patient #18

Dose level	# Patients	# DLTs
1	2	0
2	4	0
3	11	2
4	1	1

- Dose 3 recommended as MTD
- DLT percentage = 2/11 = 0.182
- Bayesian DLT prob. = 0.19, 90% CI = [0.065, 0.36]



More on discussion

- What if the first patient had DLT?
- Can we change the skeleton, e.g. add more dose level, along the terms of trial?

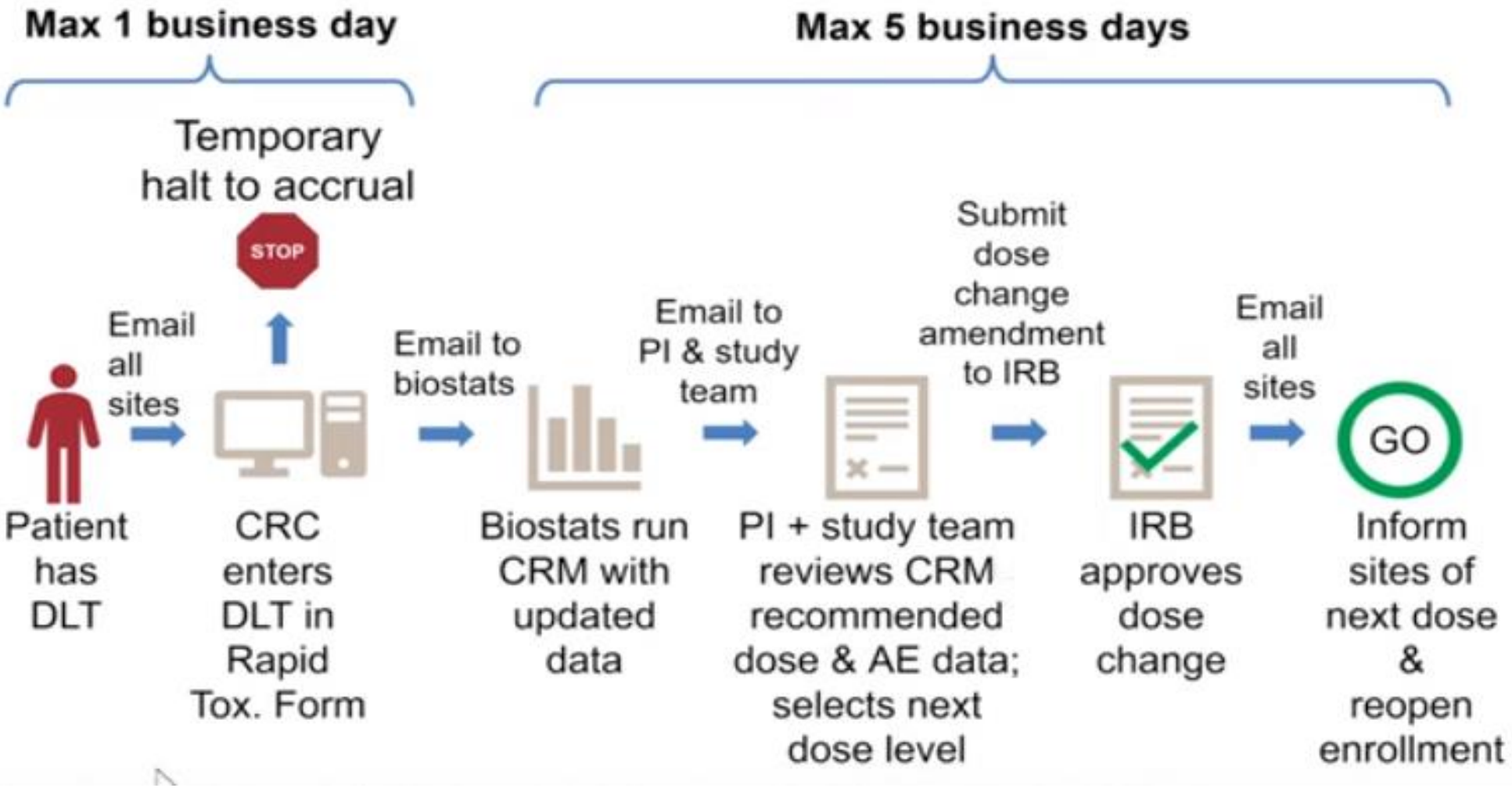
CRM Comments

Pros:

1. Achieve good estimations of the target probability of dose-limiting toxicity at the recommended dose for phase II trials without treating too many patients at suboptimal doses.
2. Flexible in DLT rate and cohort size.
3. Pre-determined sample size.
4. Use all the information to estimate MTD.

Discussion:

1. May fail to reach the recommended dose if the prior distribution are inadequate or over-bearing. => need a relatively good understanding of the drug profile.
2. Operational consideration: Require expedited collection of data from site to fit model. and require biostatistician expertise perform analysis in real time.
3. Some patients - especially the first few - may be treated at dose level higher than the intended MTD.
   => safer side effects or some side effects treatable/reversible.
   Or start with the lowest dose. However, it worsen the efficiency.
4. Will take too long to complete, as need the dose for next patient can be determined only after the result on the DLT for current patient becomes available. => more than one pts at a time. e.g. 3 pt as a cohort.
   However, may worsen the third deficiency of the CRM, its tendency to treat patients at a high dose.
   It also the challenge for other designs.



Adapted from windy London, 2022

FDA comments

- Bayesian approaches may be well-suited for some Complex Innovative Trial Designs (CIDs) intended to provide substantial evidence of effectiveness because they can provide flexibility in the design and analysis of a trial, particularly when complex adaptations and predictive models are used.
- In addition, Bayesian inference may be appropriate in settings where it is advantageous to systematically combine multiple sources of evidence, such as extrapolation of adult data to pediatric populations.
- If a sponsor chooses to submit a Bayesian CID proposal, FDA's evaluation of the proposal relies on clear communication between the sponsor and FDA regarding two areas: the prior distribution and the study decision criteria for primary and key secondary endpoints.

Interacting with the FDA on Complex Innovative Trial Designs for Drugs and Biological Products, FDA, 2020

What is BOIN?

P: The toxicity rate at the current dose

$$p = \frac{\#of\ patients\ experiencing\ DLT\ at\ the\ current\ dose}{The\ total\ \#\ patients\ treated\ at\ the\ current\ dose}$$

λ_e upper boundary; $\leq \lambda_e$ - underdosing interval

λ_d lower boundary; $\geq \lambda_d$ - overdosing interval

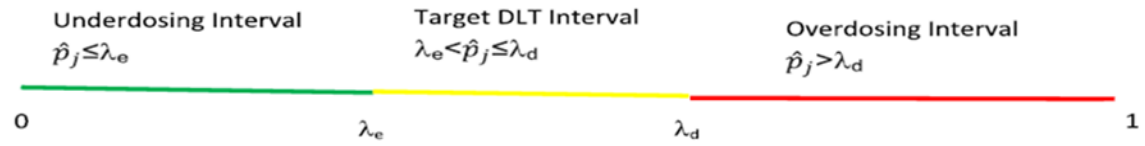
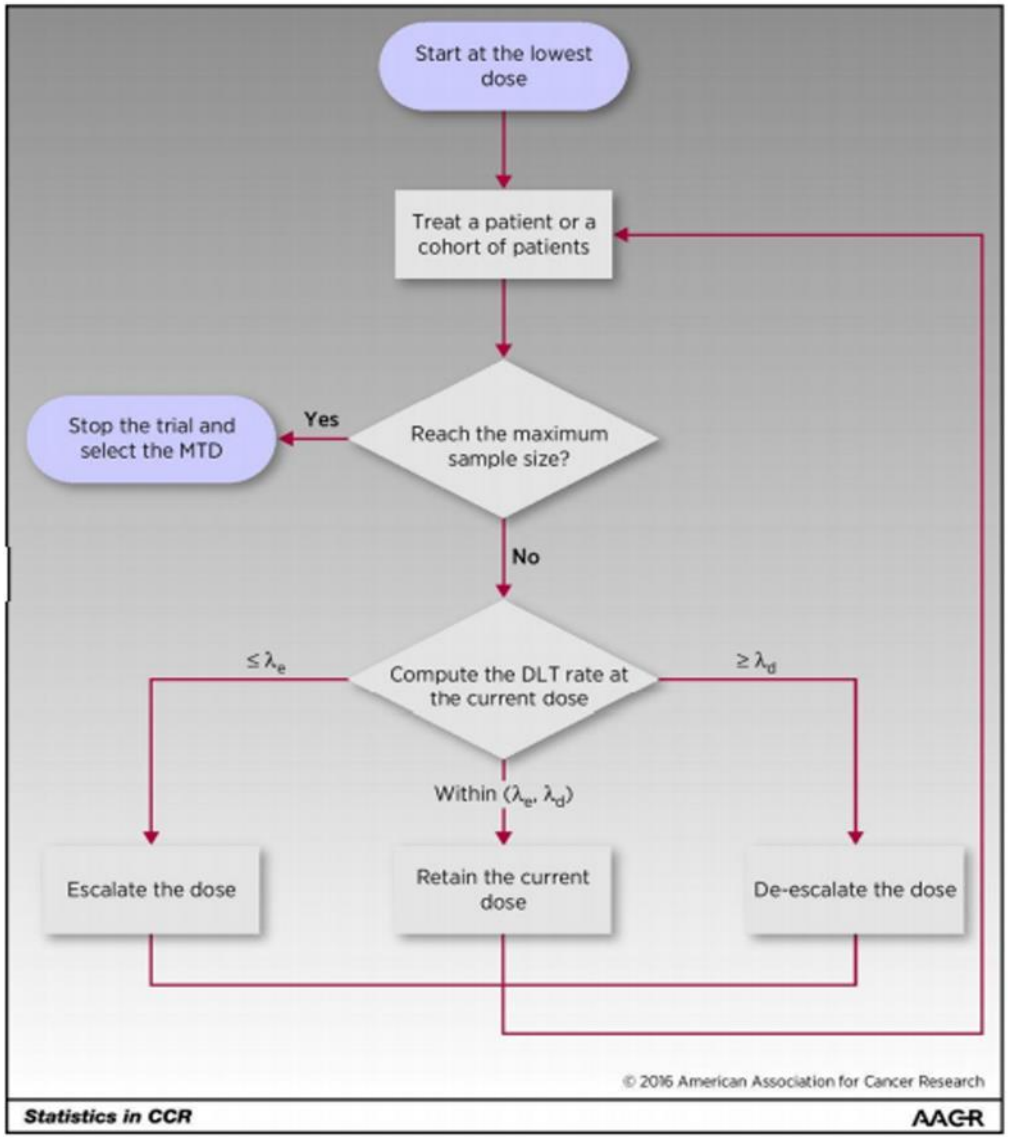


Fig. 2. Dosing Algorithm of the Basic BOIN Design (Refer to Section 2.1.1 for details).



What is BOIN? (Bayesian Optimal Interval Designs)

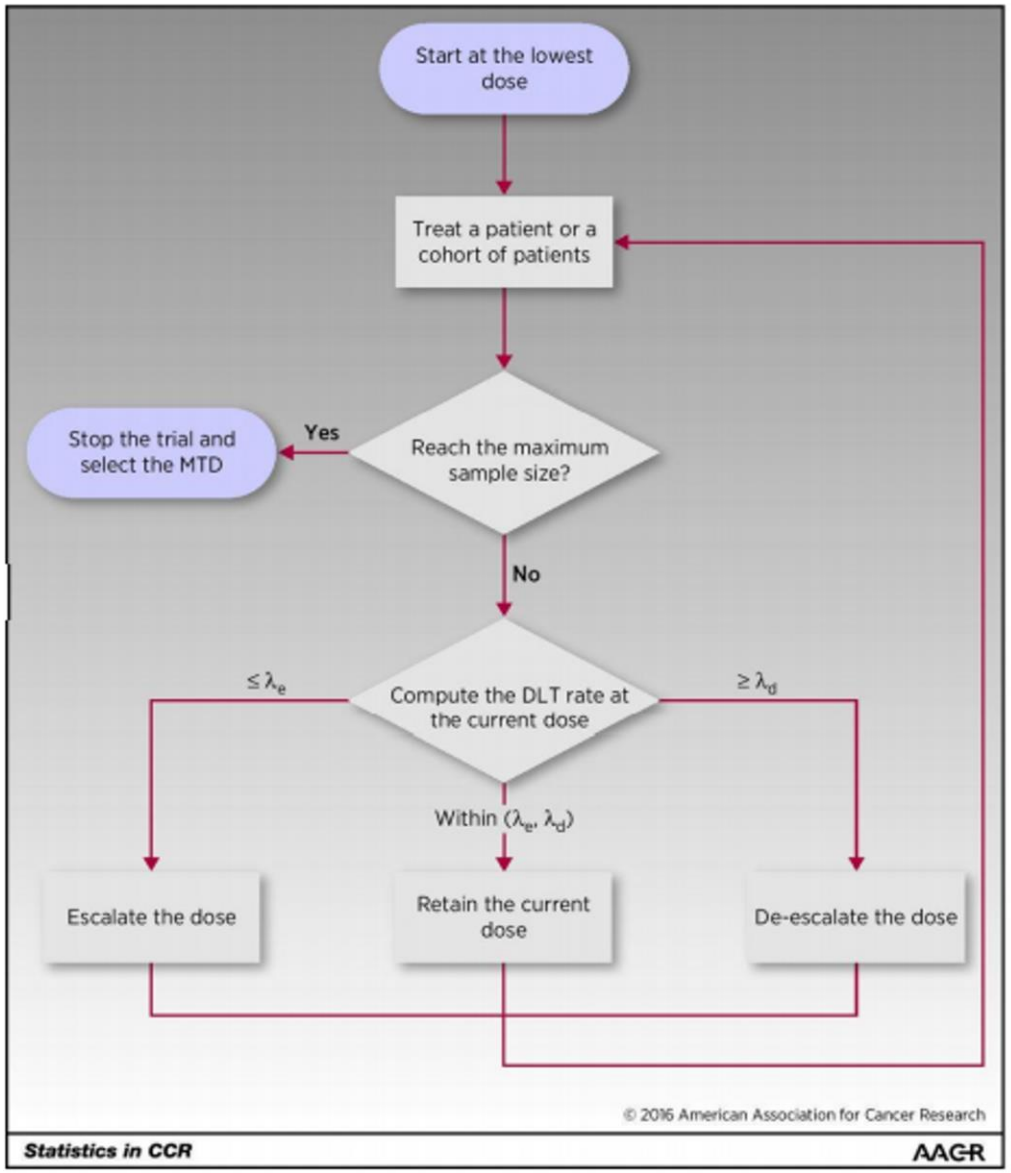
1. Treat the first patient or cohort of patients at the lowest dose. (In some trials, another dose, such as the second lowest dose, may be used as the starting dose.)
2. To assign a dose to the next patient or cohort of patients

$$p = \frac{\#of\ patients\ experiencing\ DLT\ at\ the\ current\ dose}{The\ total\ \#\ patients\ treated\ at\ the\ current\ dose}$$

P: The toxicity rate at the current dose

a. if $p \leq \lambda_e$ escalate the dose;
b. if $p \geq \lambda_d$ deescalate the dose;
c. otherwise, retain the current dose.

3. Repeat step 2 until the maximum sample size is reached.



BOIN Components

- **The decision boundary - λ_d, λ_e**

  - calculated by minimize the probability of making incorrect decision locally.

$H_{0j}: \quad p_j = \phi$ — ϕ target toxicity rate

$H_{1j}: \quad p_j = \phi_1$ — ϕ_1 the highest toxicity probability deemed subtherapeutic

$H_{2j}: \quad p_j = \phi_2$ — ϕ_2 the lowest toxicity probability deemed overly toxic

H_{0j} => current dose is MTD and should be retained => retainment(R)

H_{1j} => current dose is sub-therapeutic and should be escalated => escalation(E)

H_{2j} => current dose is overly toxic and should be de-escalated => de-escalation(D)

Incorrect decision $\bar{R}$, $\bar{E}$ and $\bar{D}$, probability of making incorrect decision:

$$\Pr(H_{0j})\Pr(\bar{R}|H_{oj}) + \Pr(H_{1j})\Pr(\bar{E}|H_{1j}) + \Pr(H_{2j})\Pr(D|H_{2j})$$

Decision error rate is minimized when

$$\lambda_{1j} = \frac{\log\left(\frac{1-\phi_1}{1-\phi}\right)}{\log\left\{\frac{\phi(1-\phi_1)}{\phi_1(1-\phi)}\right\}} \quad \text{and} \quad \lambda_{2j} = \frac{\log\left(\frac{1-\phi}{1-\phi_2}\right)}{\log\left\{\frac{\phi_2(1-\phi)}{\phi(1-\phi_2)}\right\}}$$

General guidance:

$\phi_1 = 0.6\,\phi \;\; and \;\; \phi_2 = 1.4\phi$

BOIN Components- continue

- **Pre-tabulated decision table**

	Target toxicity rate for the MTD						
Boundary	0.1	0.15	0.2	0.25	0.3	0.35	0.4
λ_e	0.078	0.118	0.157	0.197	0.236	0.276	0.316
λ_d	0.119	0.179	0.238	0.298	0.358	0.419	0.479

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Number of evaluable patients treated	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
Deescalate 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

Yuan et al, 2016

BOIN Components- continue

- **Safety stopping rule** is calculated by a model:

  Suppose j is the current dose level. If $P\left(p_j > \Phi\middle|y_j, n_j\right) > 0.95$, and $n_j \geq 3$,dose level j and higher doses are eliminated from the trial. The trial is terminated if the lowest dose is eliminated.

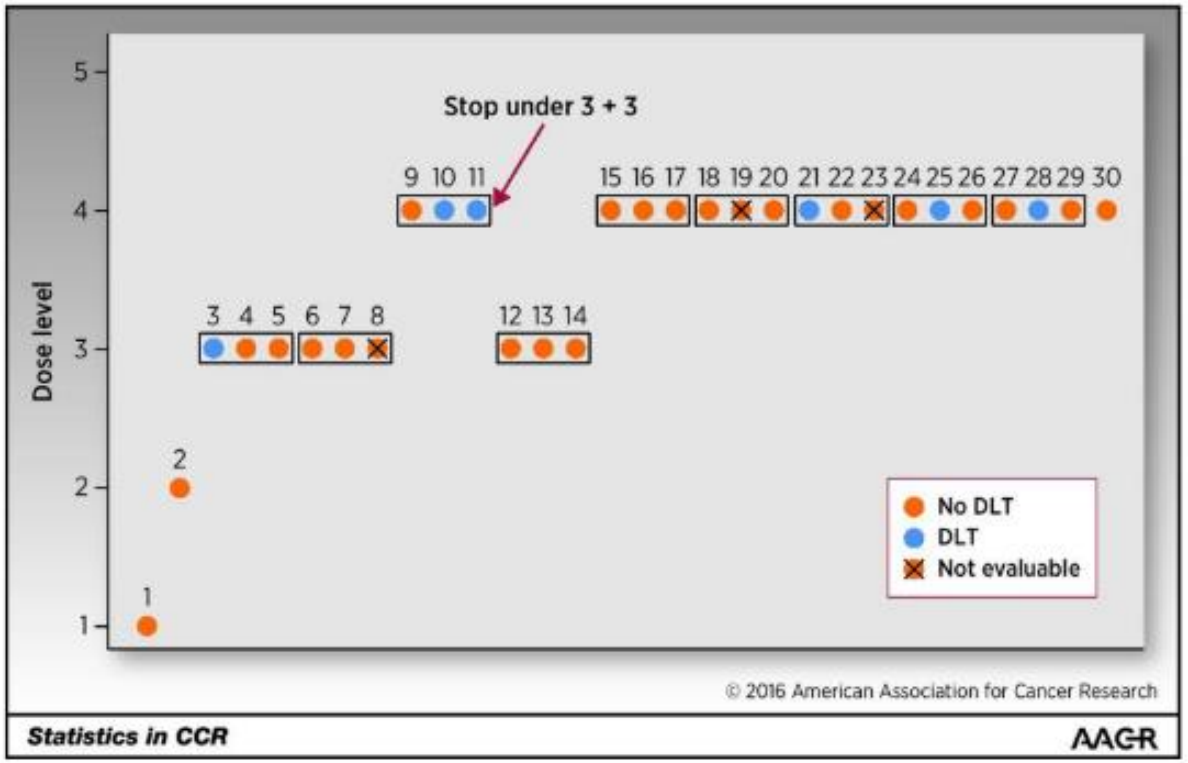
- **MTD** were determined by pooling data from across dose.

  Select MTD dose for which the isotonic transformed values ($\tilde{\boldsymbol{p}}$) of the DLT rate is closest to the target.

  If there are ties, we select from the ties the highest dose level when $\tilde{\boldsymbol{p}}_j < \phi$ or the lowest dose level when $\tilde{\boldsymbol{p}}_j > \phi$.

Example BOIN

- DLT rate = 30%
- 5 prespecified doses
- 30 patients
- ATD design
- MTD selection:
  - BOIN: DL4; DLT rate = 5/17 =29.4% (95% CI: 0.10–0.56)
  - 3+3: DL3; DLT rate = 20% (95%CI: 0.005-0.72)



	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Number of evaluable patients treated	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
Deescalate 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

Yuan et al, 2016

Practical use

A phase1b/2 study to evaluate the safety and effectiveness of Onvansertib in combination with Paclitaxel in breast patients.

Primary Objective:

Phase 1b

- Safety, characterization of DLTs (End points: AE rate, DLT observation rate)
- Determination of RP2D

Phase 2

- Determine the objective response rate (endpoint: ORR) of the combination utilizing RECIST 1.1 criteria.

Sample size: 50-60

Designs:

BOIN(Phase 1b) + Single arm Simon's two-stage (phase 2)

BOIN: Sample size 24, 3 pt as a cohort/3 dose levels/Start with dose level 1

Simon's two-stage: Sample size 34/ Stop for futility

BOIN Comments

Pros

- Can determine the next dose, but don't have the statisticians re-running the model each time, easier to implement compare with CRM. Dose escalation and de-escalation rule can be tabulated before the onset of trial. (compare with CRM).
- Simulation: risk of poor allocation(more on MTD), risk of high toxicity(more DLT than target MTD). - Ethical consideration
- Flexible in DLT and cohort size. And cohort size can change along the trial
- Pre-specified sample size in BOIN. Sample size can be pre-determined in BOIN.
- More likely to accurately select the MTD, with lower risk of overdosing (compare with CRM) and allocate more patients to the MTD (compare with 3+3).
- Handle a passive change in cohort size. - Some patients may become invaluable due to relapsed disease or transplant.

Discussion

- Prolonged toxicity outcomes: It requires toxicity to be quickly ascertained with respect to the accrual time.
- Testing a drug with known MTD in other diseases.

  Know where to start and may not need to test more than 3 dose levels. If <= 3 candidates, go 3+3.
- Intra-patient dose modification permitted and not part of DLT evaluation.

  E.g. modify dose level based on concomitant drug use or patient condition

FDA comments

- Under the non-informative prior, the local BOIN design, in its revised form, can be designated fit for-purpose.
- But, as with other methods, the performance of BOIN is affected by the choice of design parameters. If any underlying assumption is violated, the BOIN method may not be able to estimate the dose toxicity relationship accurately. For example, in instances with combination therapy, where the dose-toxicity relationship may not be monotonically increasing or also in the case of therapies with delayed onset of toxicities.

  Also, a problem in 3+3 and CRM.

Model based or Rule based?

Model Based

Advantages:

- More Flexibility. e.g. in target DLT rate and cohort size.
  - 3 + 3 accept MTD range from (1/6– 1/3)
- Use all available information from patients to estimate MTD. => narrower CI
- Pre-determined sample size.
- Handle passive patient loss. (if loss patient, can still determine the next dose level)
- Possibility to address the unmet challenges:
  - Take into account late-onset toxicities (TITE CRM, TITE BOIN).
  - Take into account both toxicity and efficacy (EffTox + TriCRM, BOIN-EF, BOIN12).

Limitations:

- Harder to understand and implement.

Rule-Based

Advantages:

- Clear, transparent and widely accepted.
- Safe.

Limitations:

- No flexibility in # patients per dose and MTD rate.
- Large variability in MTD determination.
- # of doses affects performance.

Unmet needs

- In phase I clinical design(Oncology), we have a hidden assumption that:

  Toxicity Monotonicity : pi ≤ pi+1.

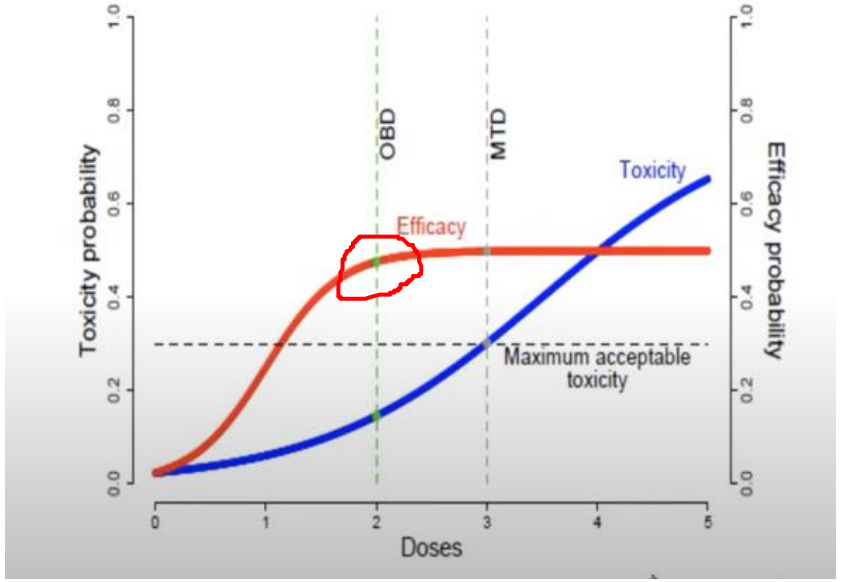
  Efficacy Monotonicity : qi ≤ qi+1 – if not, why escalate when the dose is safe?

  However, in many of the newer drugs, although the toxicity of the drug increases with an increase in dose, the efficacy of the drug does not always increase and could plateau at a lower dose. In these cases, it is imperative to find a dose that is optimal for both safety and efficacy to maximize the risk-benefit trade-off.

- Prolonged toxicity.

  The proposed primary endpoint is ORR by Tomer that may take ~4 months to occur. Expected mOS is ~9 months (if treated with 10mg).

  Will take forever to finish this phase I trial.



Adapted from Yuan Ji, 2018

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Thank You!