



Sumptuous Data Sciences

Common sample size estimations for Phase I Clinical Trials

Suryaprakash Kavalipati

Aayush Bhoraskar

Phase I Trials

- Dose escalation studies to establish MTD/RP2D.
- Typically assumed higher dose reflects higher efficacy, and monotonous dose-toxicity relationship.
- Generally consider the highest dose with DLT rate less than an established percent (e.g. 33%).
- DLT=Dose Limiting Toxicity. According to NCI, adverse reactions that are deemed serious enough to prevent an increase in dose or level of treatment.
- MTD=Maximum Tolerated Dose. Highest dose with DLT rate less than pre-determined unacceptable rate.
- RP2D=Recommended Phase 2 Dose. The dose recommended by dose review committee to be considered for Phase II clinical trials.

Dose Escalation Designs

Rule Based Design

- 3 + 3 design and its variants
- Accelerated titration design
- Pharmacologically Guided Dose Escalation

Model Based Design

- Continual Reassessment Method (CRM)
- Bayesian Logistic Regression Method (BLRM)

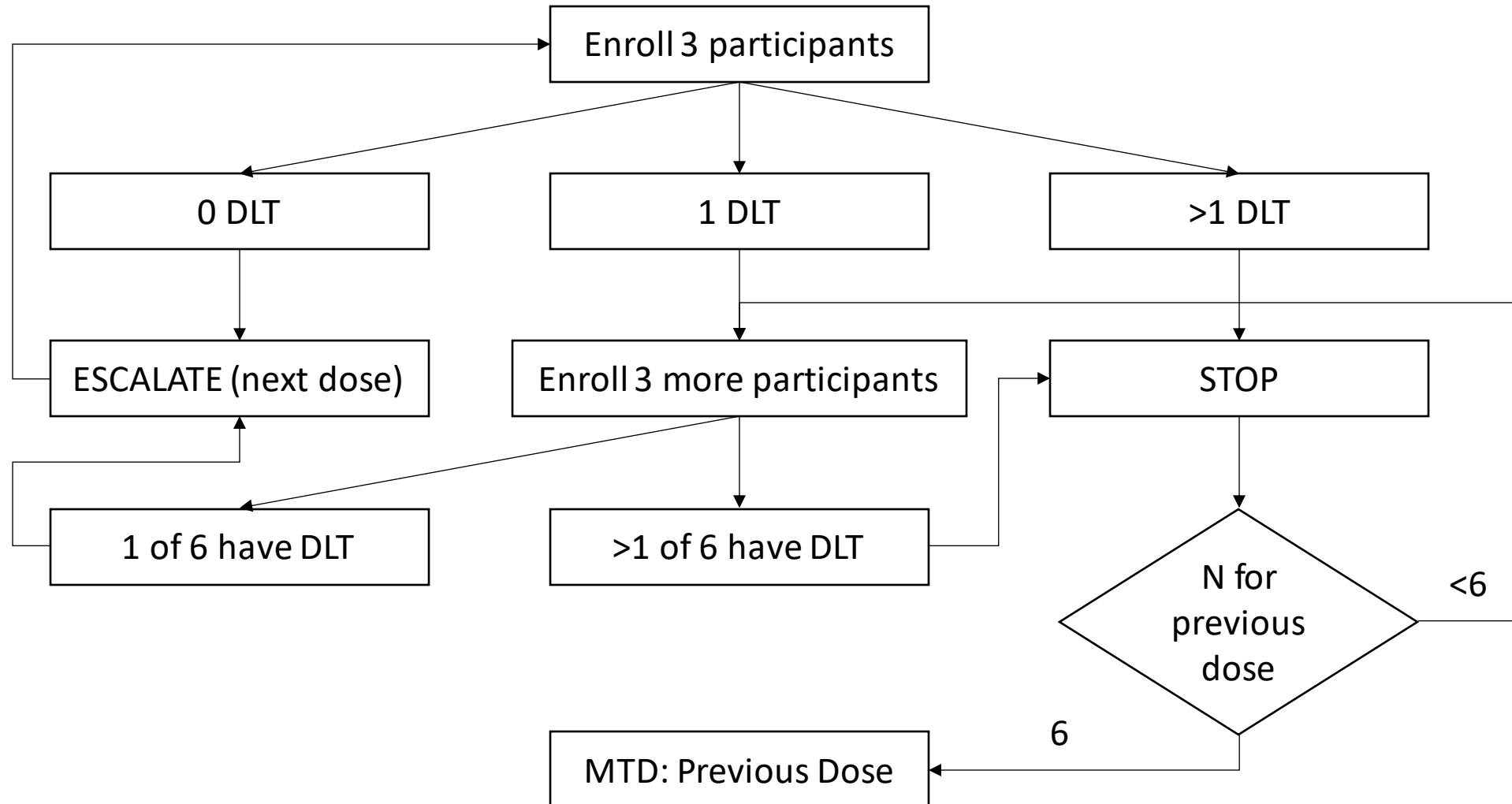
Model-Assisted Design

- Modified Toxicity Probability Interval (mTPI) Design
- Bayesian Optimal Interval Design (BOIN)
- Keyboard Design

3 + 3 design



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3 + 3 design

- Traditionally, modified Fibonacci sequence used for dose increments.
 - Most commonly, modified depending on formulations, PK and SRC review.
- Typical starting dose: $1/6^{\text{th}}$ of HNSTD in animal models.
- Modified 3 + 3 designs developed
 - 2+4: add 4 participant cohort if 1 of 2 have DLT.
 - 3+3+3: add 3rd cohort of 3 if 2 of 6 have DLT.
 - 3+1+1: add 1 if 1 or 2 DLT observed in 1st cohort of 3. Add another if 2 of 4 have DLT.

3 + 3 design

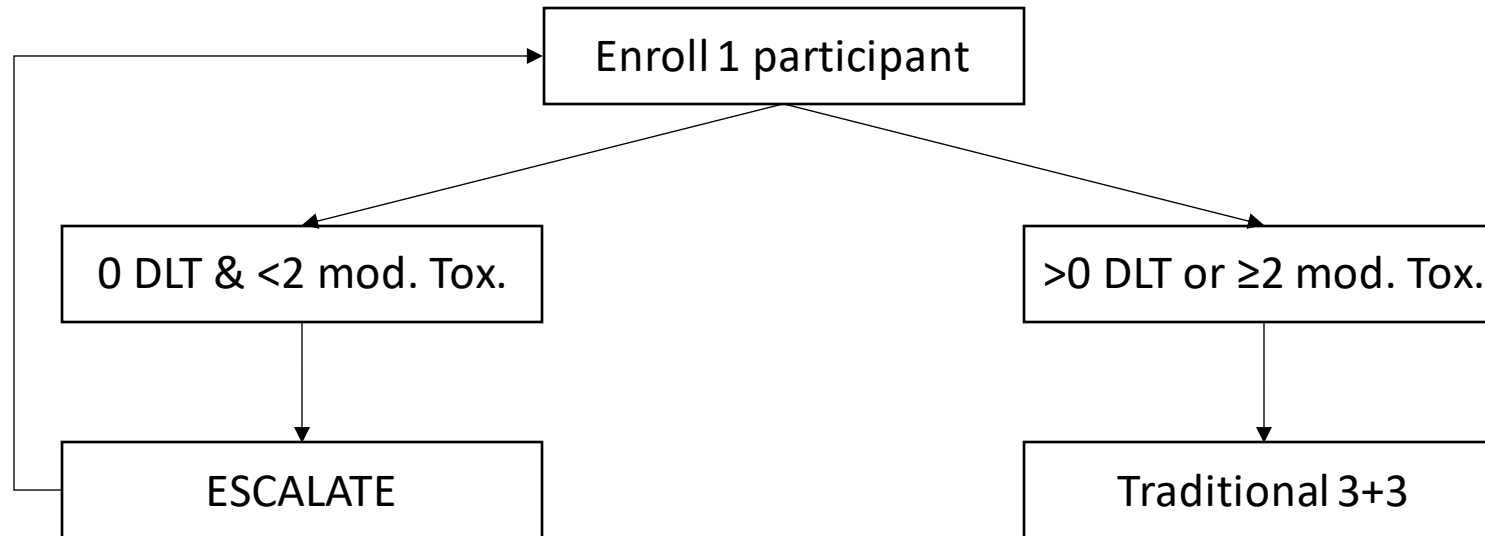
Pros

- Easy to design and implement
- Safe design
- PK interpatient variability
- No modeling requirement

Cons

- Sub-therapeutic dosing in high proportion of participants
- Low MTD accuracy
- Works only with targeted 33% DLT rate
- Only result from 1 dose utilized for determination of next dose.

Accelerated Titration Design



- Not commonly used in Clinical studies.
- Intra-patient dose escalation allowed.
- Idea is to reduce the sub-therapeutic dose exposure.

Continual Reassessment Method (CRM)

- Target DLT rate defined.
- Bayesian method. *Priori* DLT probabilities determined for each dose level to have initial dose-toxicity model. *Posterior* probabilities generated at dose level as patients are enrolled.
- Dose-toxicity model updated frequently along with DLT probability estimation.
- MTD: Dose with highest DLT probability less than target DLT rate.
- Can overestimate the MTD
- High dependence on initial (prior) DLT probabilities for dose levels.
- Computationally intense, might require use of specific software.



Bayesian Logistic Regression Model (BLRM)

- Type of modified CRM.
- Uses EWOC (Escalation with Overdose Control) principle. Basically probability of overdosing (DLT probability for overdose is pre-defined) less than a pre-determined probability (usually 25%).
- Contrary to CRM model (which uses 1-parameter model), BLRM uses a 2-parameter model.
- Not as dependent on initial (prior) DLT probabilities for dose levels as CRM model.
- Escalation/De-escalation recommendation provided by model, but decision is clinically driven.
- Not necessarily better than rule-based design (e.g. 3+3) when few dose levels.

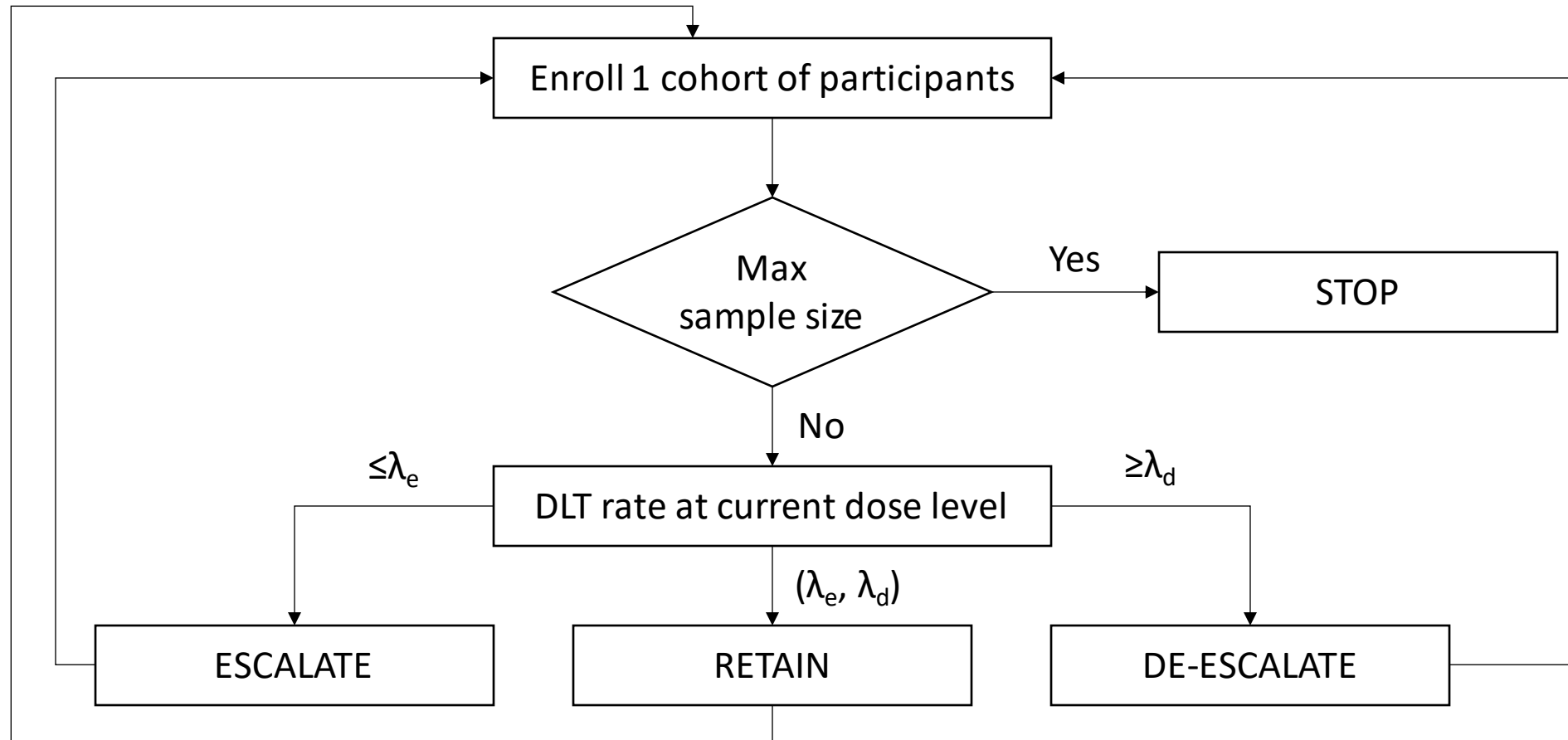
Bayesian Optimal Interval Design (BOIN)

- Model-assisted design. Specific dose escalation/de-escalation rules but decision making based on a statistical model.
- Maximum sample size pre-determined (usually 30).
- Dose escalation (λ_e) and de-escalation (λ_d) boundaries determined based on target DLT rate (Φ), highest sub-therapeutic DLT rate (usually 0.6*target DLT rate, Φ_1), and lowest overdose DLT rate (usually 1.4*target DLT rate, Φ_2).

$$\lambda_e = \frac{\log \frac{1-\Phi_1}{1-\Phi}}{\log \frac{\Phi(1-\Phi_1)}{\Phi_1(1-\Phi)}} \quad \lambda_d = \frac{\log \frac{1-\Phi}{1-\Phi_2}}{\log \frac{\Phi_2(1-\Phi)}{\Phi(1-\Phi_2)}}$$



Bayesian Optimal Interval Design (BOIN)



Comparison of Some Common Designs

	3 + 3 design	BLRM	BOIN
Type	Rule-based	Model-based	Model-assisted
MTD accuracy	Low	High	High
DLT Rate	33%	Flexible	Flexible
De-escalation	Only to establish MTD if current dose has >1 DLTs and previous dose has <6 participants	Allowed	Allowed
Re-escalation	Not Allowed	Allowed	Allowed
Cohort Size	3	Flexible	Flexible
Implementation	Easy	Complex	Easy
Decisions	Pre-defined rules	Clinically driven (model provides non-binding recommendations)	Pre-defined rules



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