Establish the Maximum Tolerated Dose in Phase-I Trials using 3+3 Method

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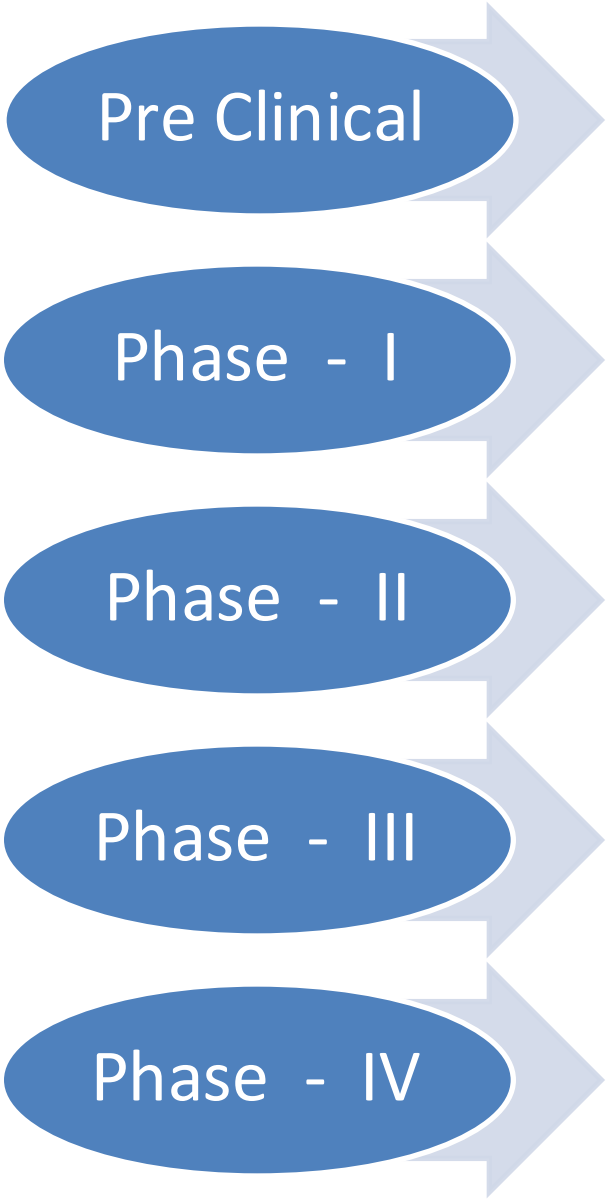
Agenda

- Introduction to Phase-1 trials
- Dose Escalation Studies
- 3+3 design for finding Maximum Tolerated Dose
- Case Study for finding Maximum Tolerated Dose
- SAS® Macro for Simulating 3+3 Design
- Limitations of 3+3 Design

Phases of a Clinical Trial



Initial testing done in lab or with animals

Find the safest dose
Find most effective way to administer a dose

Checking for Safety and Effectiveness

Confirmatory Phase

Post Marketing Surveillance

Phase-I Trials

Aim → Maximum Tolerated Dose **(MTD)**

MTD → The highest dose of a treatment that does not cause unacceptable side effects.

DLT → Dose Limiting Toxicity.
Unacceptable side effects or toxicity.

Phase-I Trials

- Phase-I trials are first trials conducted on humans.

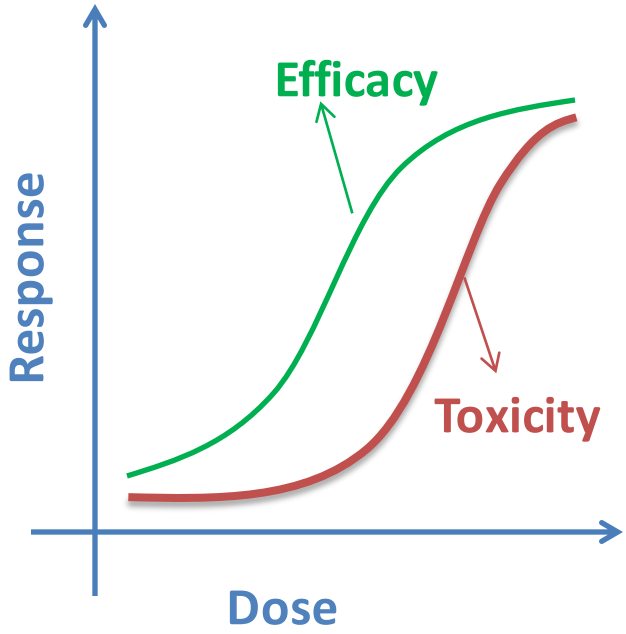
- Usually these trials include healthy volunteers.

  But there are circumstances when real patients are used, such as oncology trials.

Phase-I Trials

- An increased dose is associated with increased chance of clinical efficacy.

- Phase I trials are designed as a dose-escalation study to determine the MTD.



Dose Escalation Studies

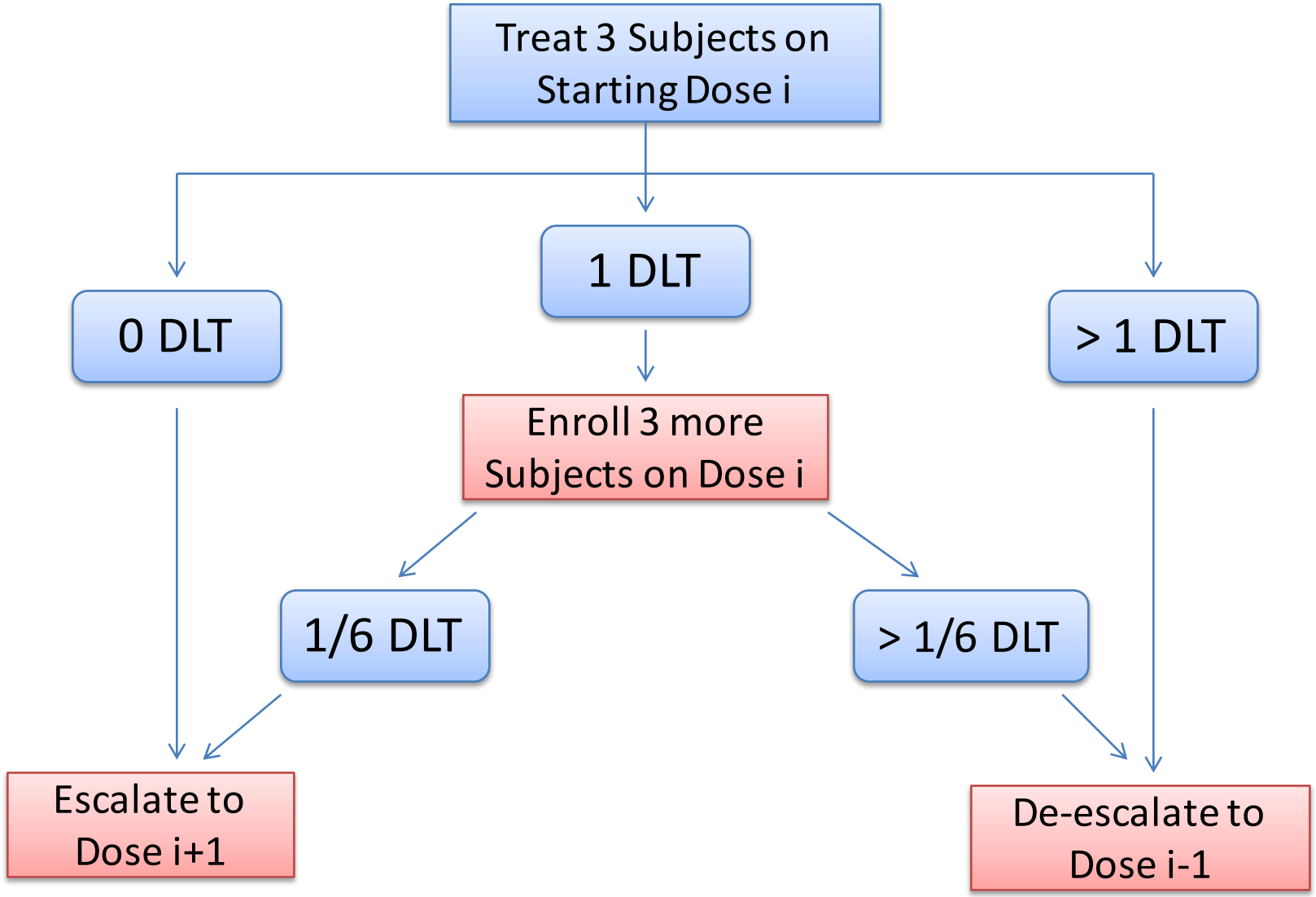
- Minimize the number of patients exposed to toxic doses, while identifying the MTD.

- Dose escalation methods fall into two broad classes:
  - Rule Based Design
  - Model Based Design

- Rule-based designs allow dose escalation and de-escalation depending on the absence or presence of DLTs in the previous cohort of treated subjects.
- The most widely used rule based design is the **3+3 design**.

3+3 Design

Algorithm of a traditional 3+3 Design



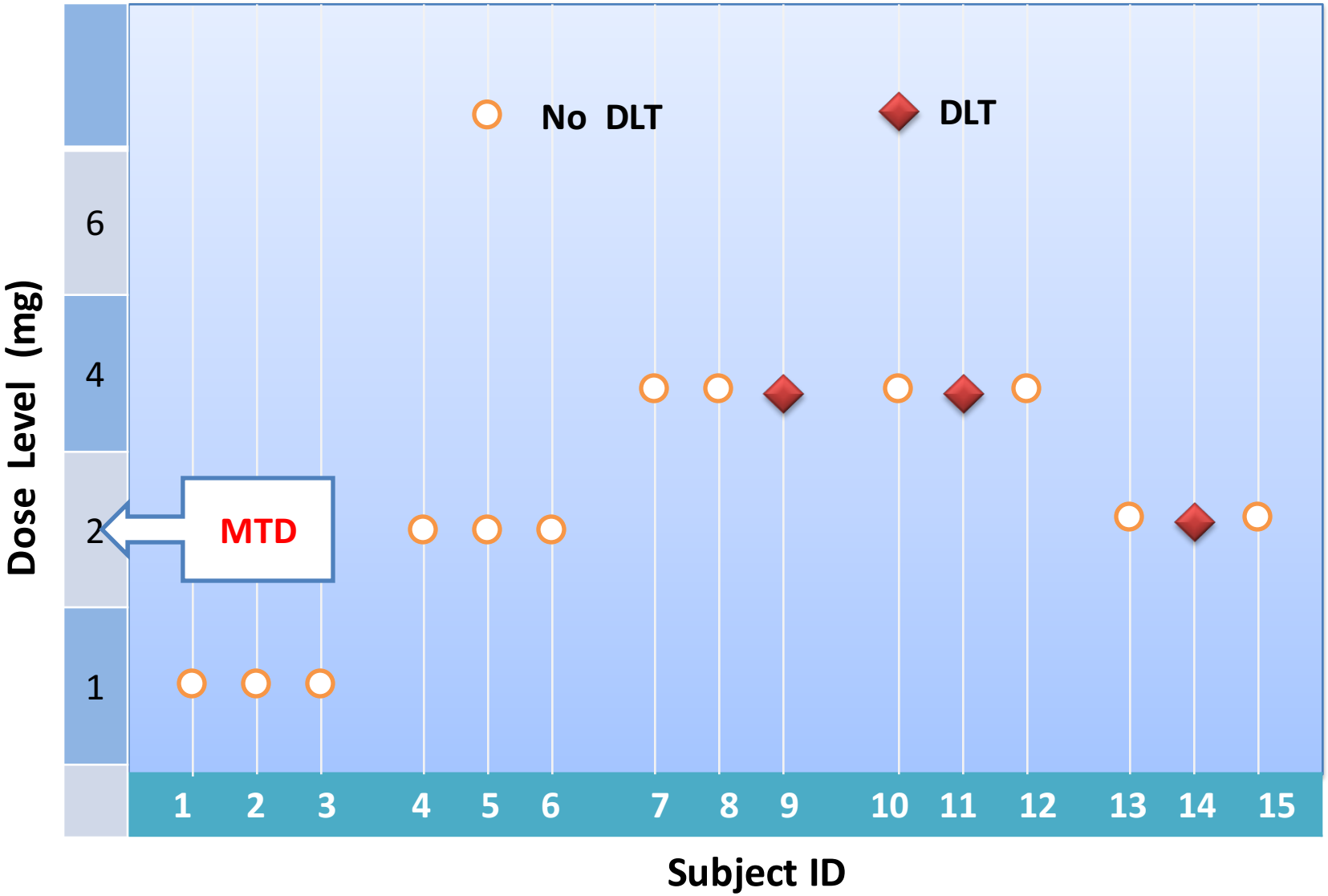
Case Study

- A study was conducted to determine the MTD of ***HB-110***, a vaccine administered by Electroporation in chronic hepatitis B patients.

- The 3+3 design was used to reach the MTD.
  - Subjects were observed for a minimum of 28 days.
  - Each subject was administered HB-110 per day.
- The dose-levels of HB-110 used were 1mg, 2mg, 4mg & 6mg.

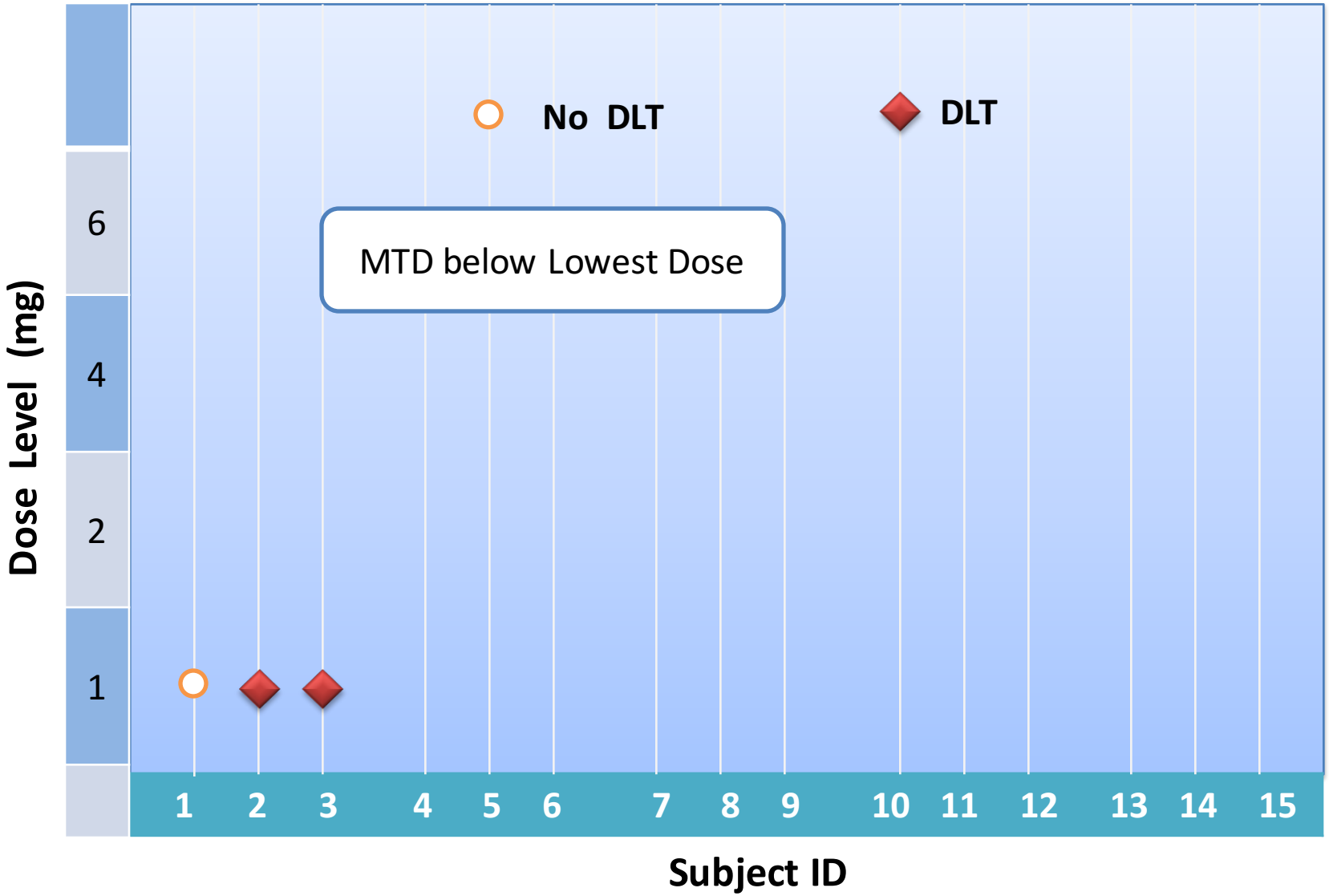
Case Study

Per Subject Response in the trial



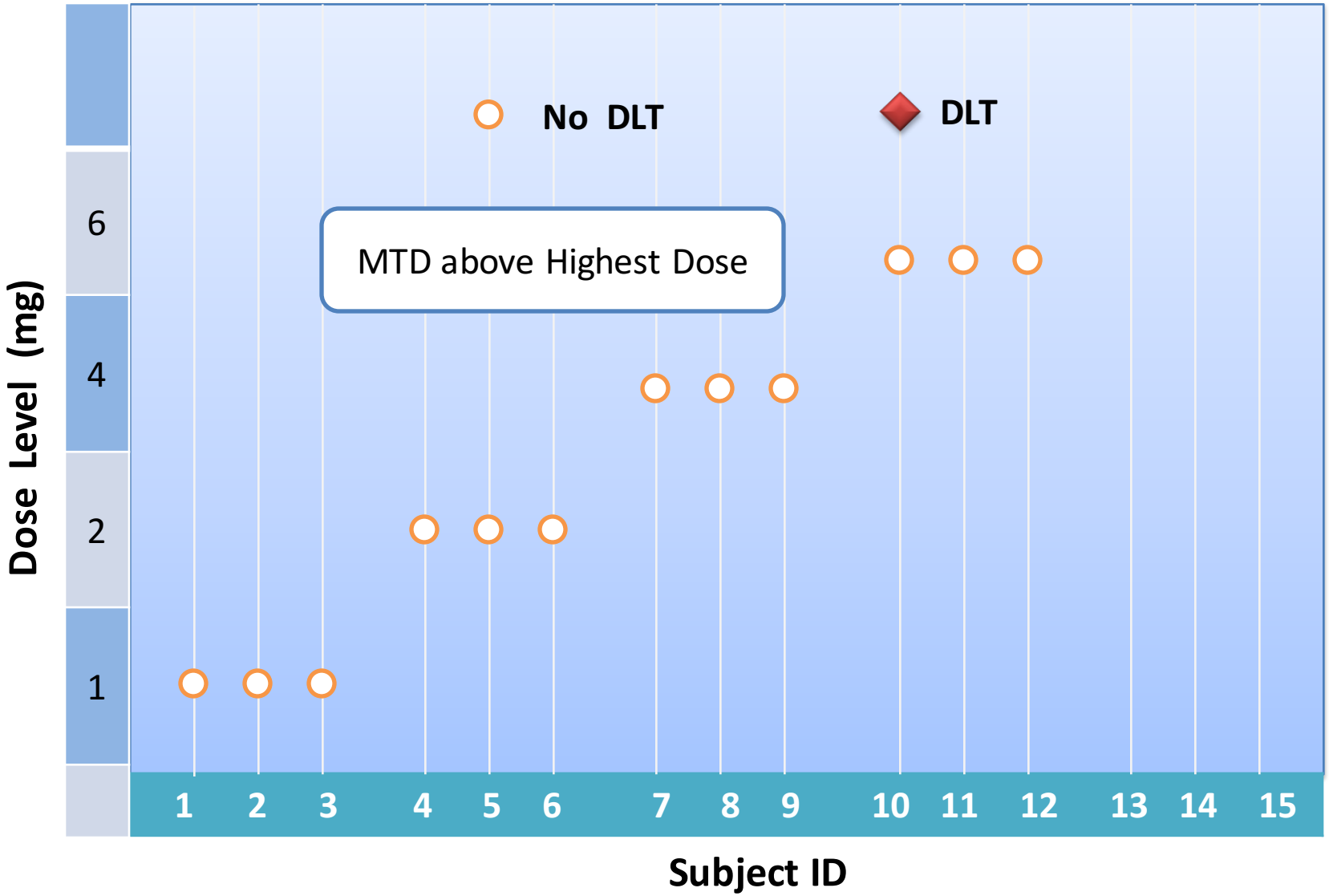
Case Study

Unable to find the MTD



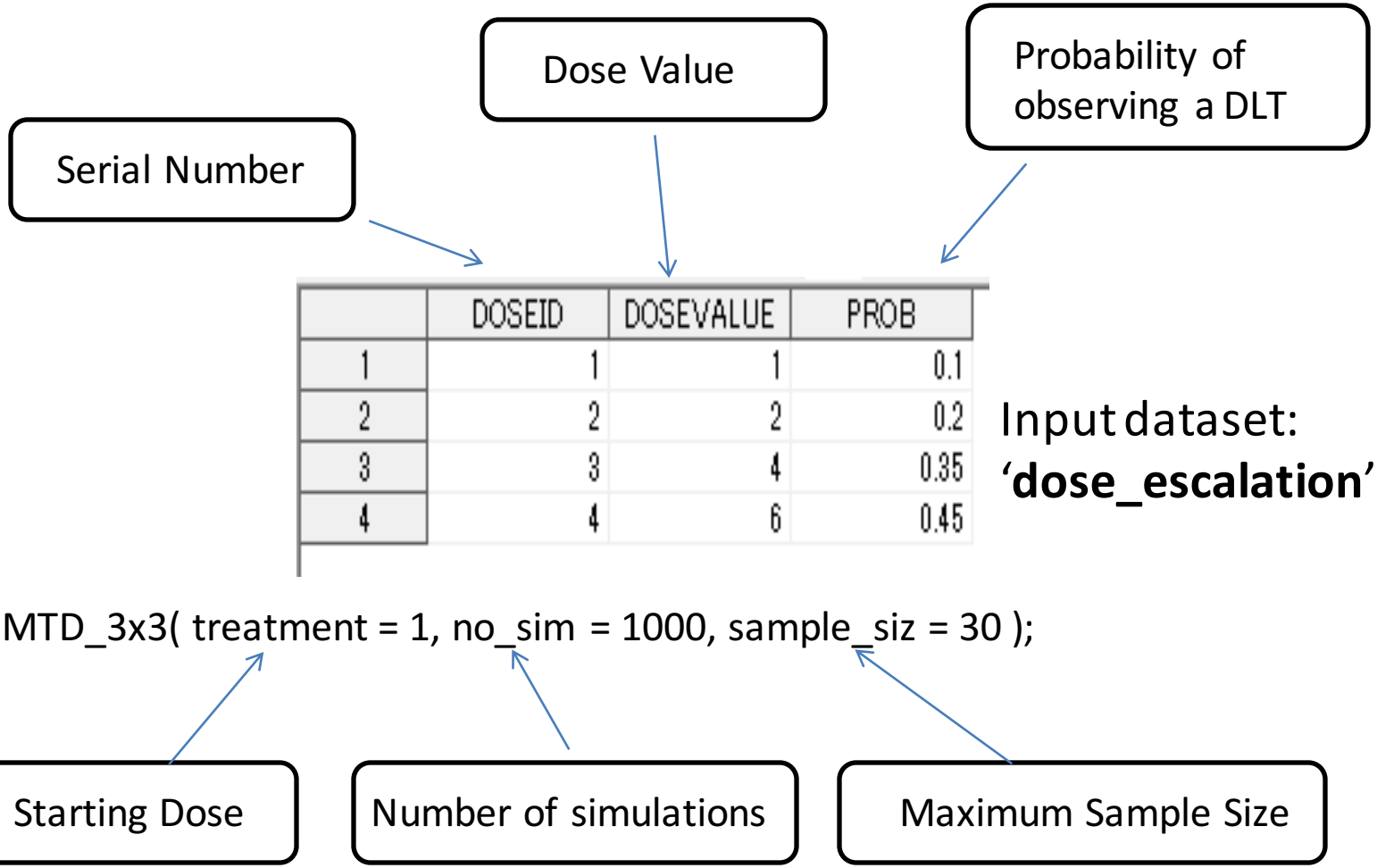
Case Study

Unable to find the MTD



SAS Macro

The macro simulates a 3+3 Design



	DOSEID	DOSEVALUE	PROB
1	1	1	0.1
2	2	2	0.2
3	3	4	0.35
4	4	6	0.45

Input dataset: '**dose_escalation**'

```
%MTD_3x3( treatment = 1, no_sim = 1000, sample_siz = 30 );
```

Starting Dose

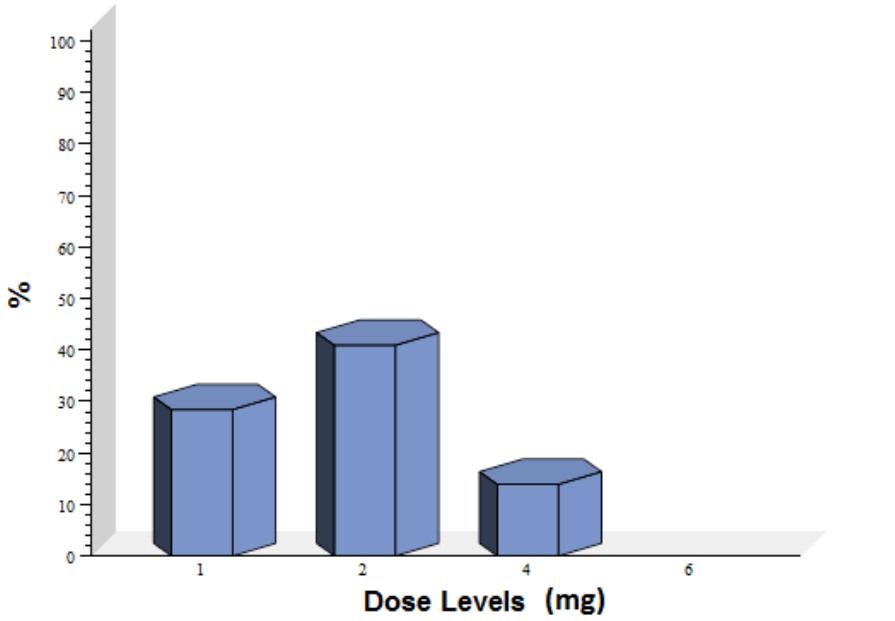
Number of simulations

Maximum Sample Size

SAS Macro

Output dataset:
'Simulation_summary'

	mtd	count	percent
1	1	284	28.4
2	2	409	40.9
3	4	139	13.9
4	6	0	0
5	MTD below lowest Dose	112	11.2
6	MTD above highest Dose	56	5.6
7	Inadequate SS	0	0



Limitations

- The design is inflexible.
- Decisions are not based on outcomes from all recruited subjects.
- Many subjects are treated at doses lower than MTD while few subjects actually receive the MTD.

These limitations are overcome by model based designs like
CRM(Continual Reassessment Method)
BLRM(Bayesian Logistic Regression Method)

Summary

- 3+3 remains the most popular method because of its simple concept and operational ease.
- It can be implemented without any complex statistical considerations and computations.
- 3+3 design is used as a starting step for carrying out more complex designs.

References

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Case Study : "Tolerability, Immunogenicity and Efficacy of HB-110 Administered by Electroporation in Chronic Hepatitis B Patients." https://clinicaltrials.gov

THANK YOU

QUESTIONS