

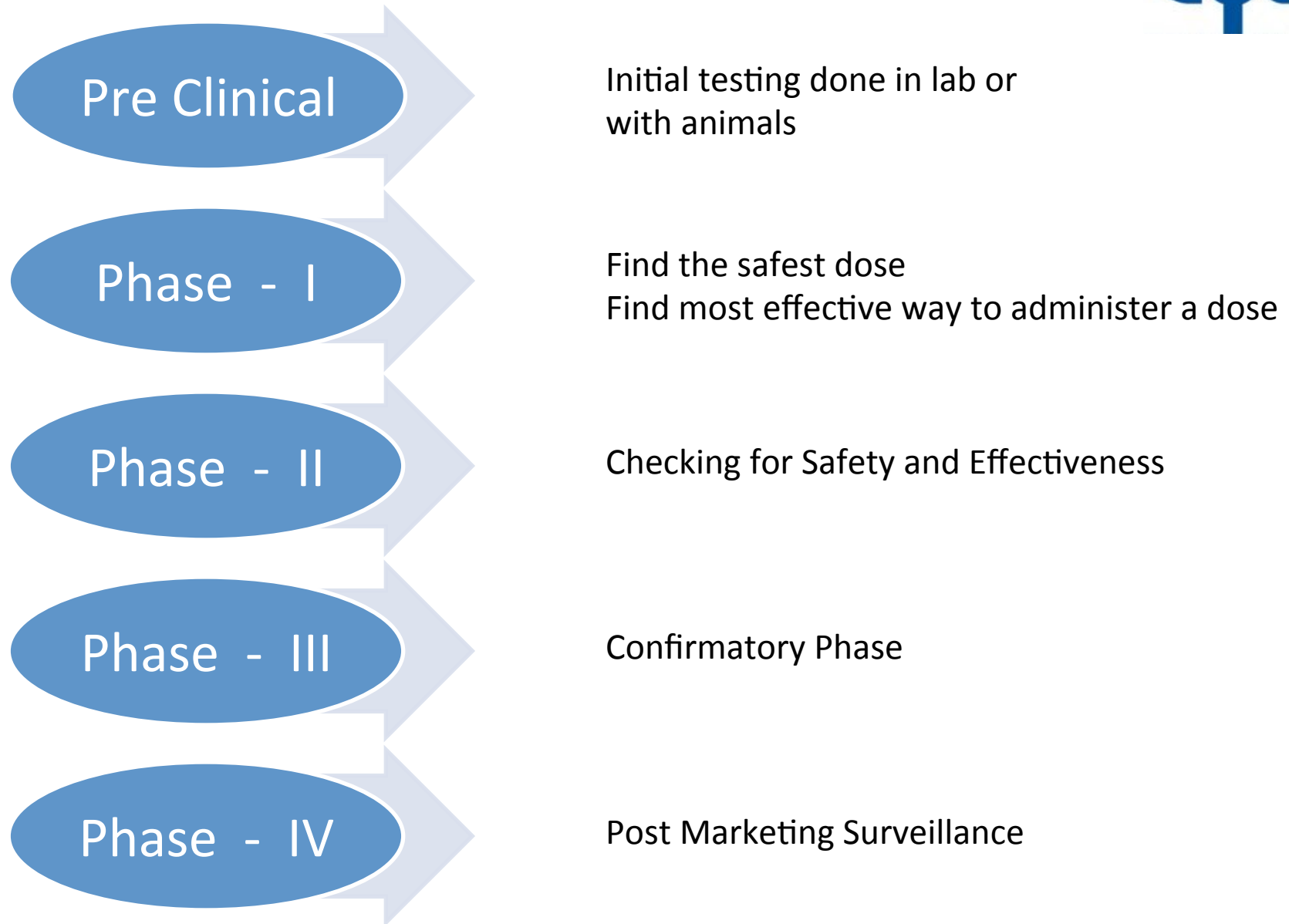
Establish the Maximum Tolerated Dose in Phase-I Trials using 3+3 Method

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- 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



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.

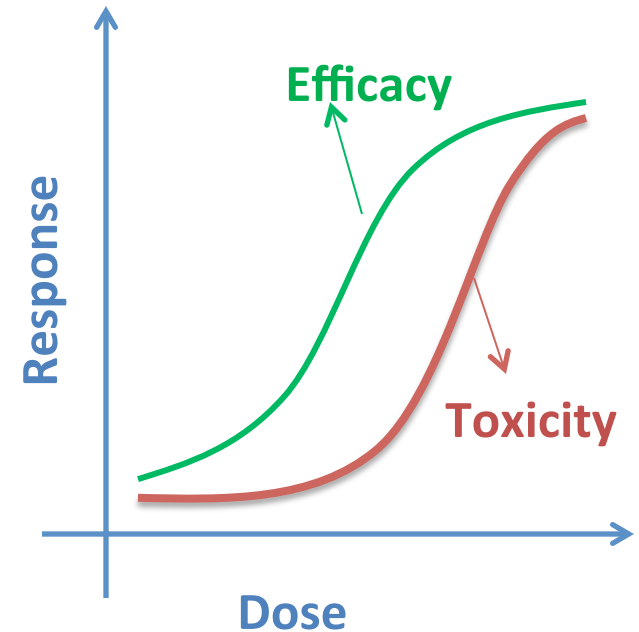
Phase-I Trials

- 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

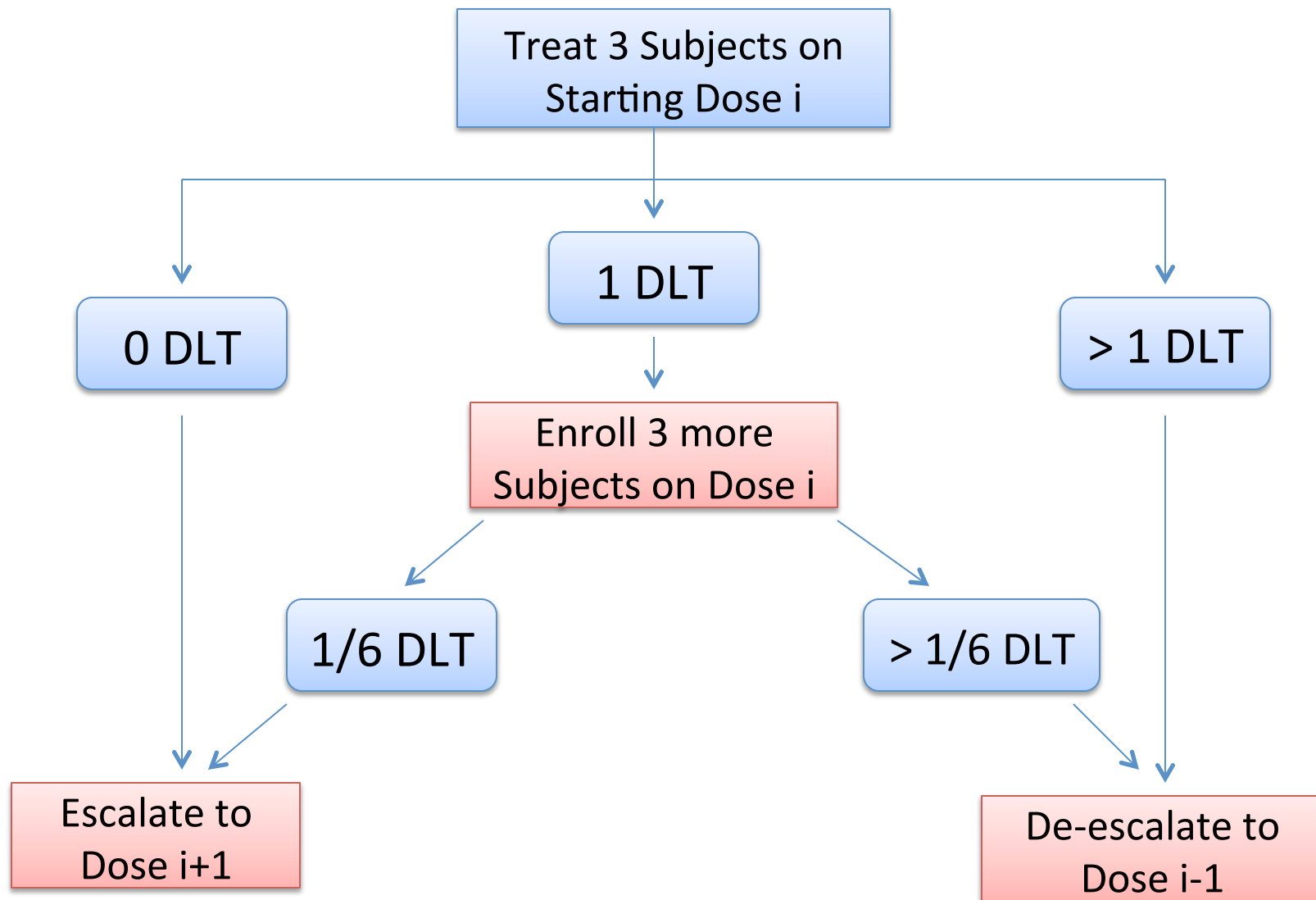
- An increased dose is associated with increased chance of clinical efficacy.
- Phase I trials are designed as a dose-escalation study to determine the MTD.



- 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



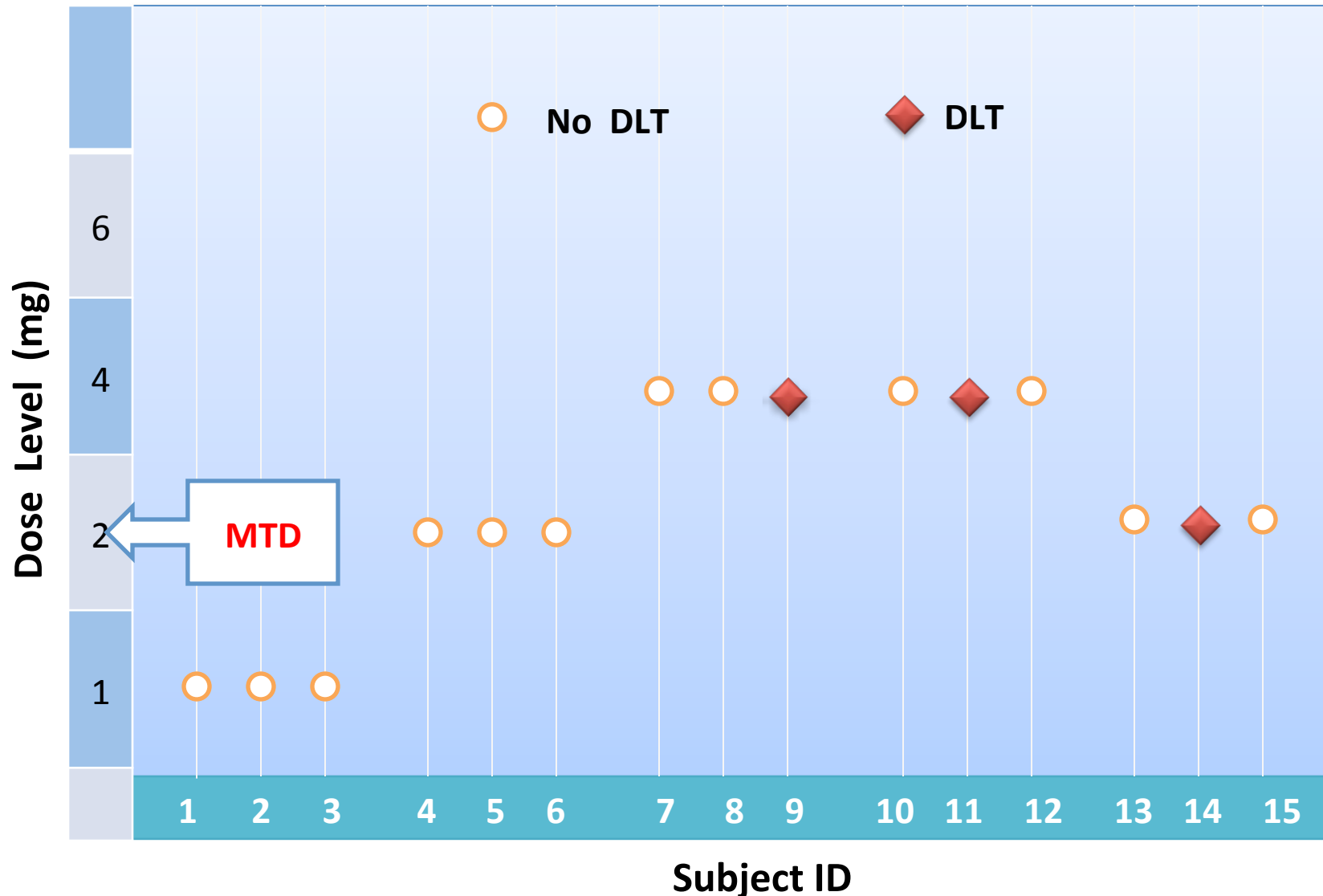
- A study was conducted to determine the MTD of **HB-110**, a vaccine administered by Electroporation in chronic hepatitis B patients.



- 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.

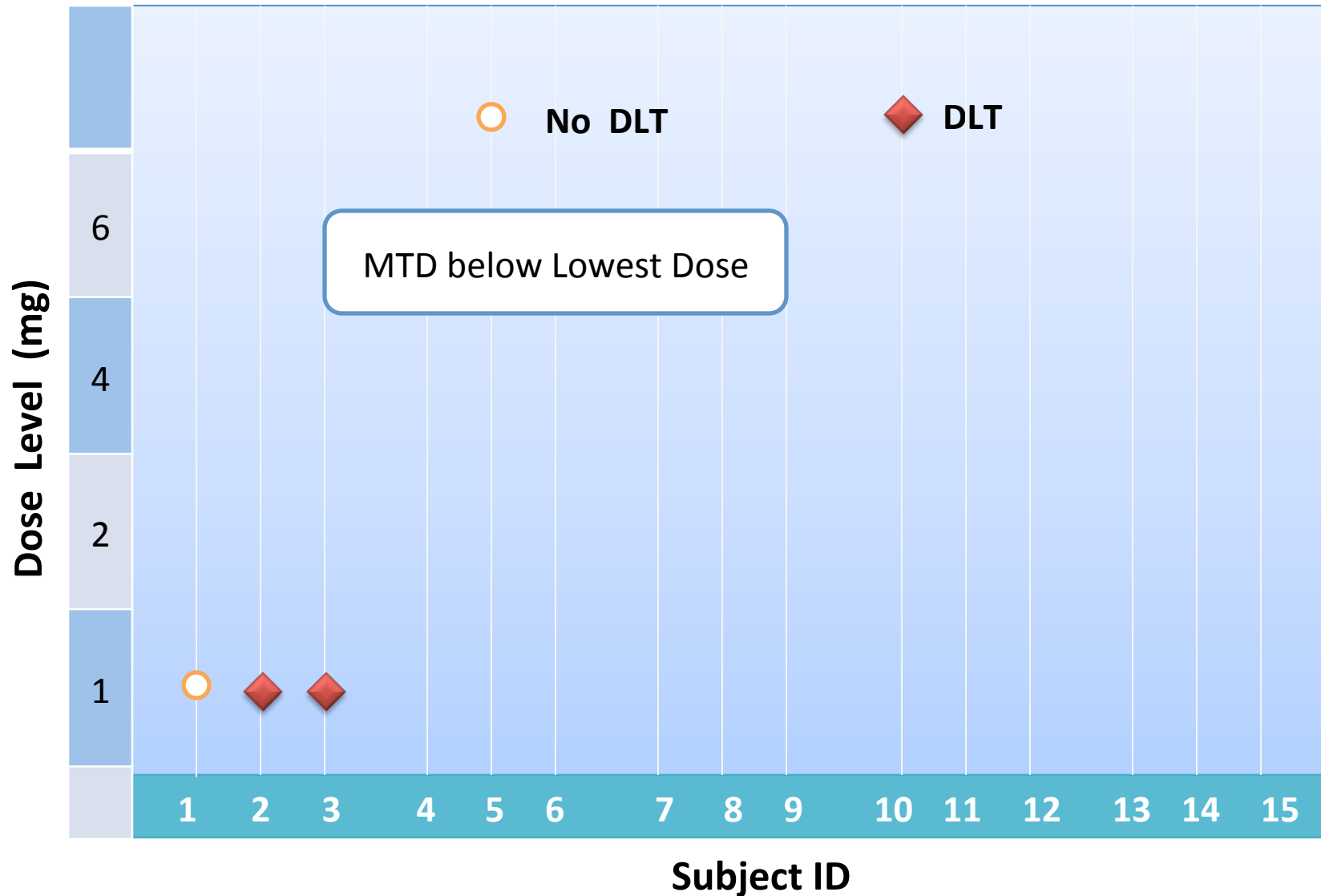
Case Study

Per Subject Response in the trial



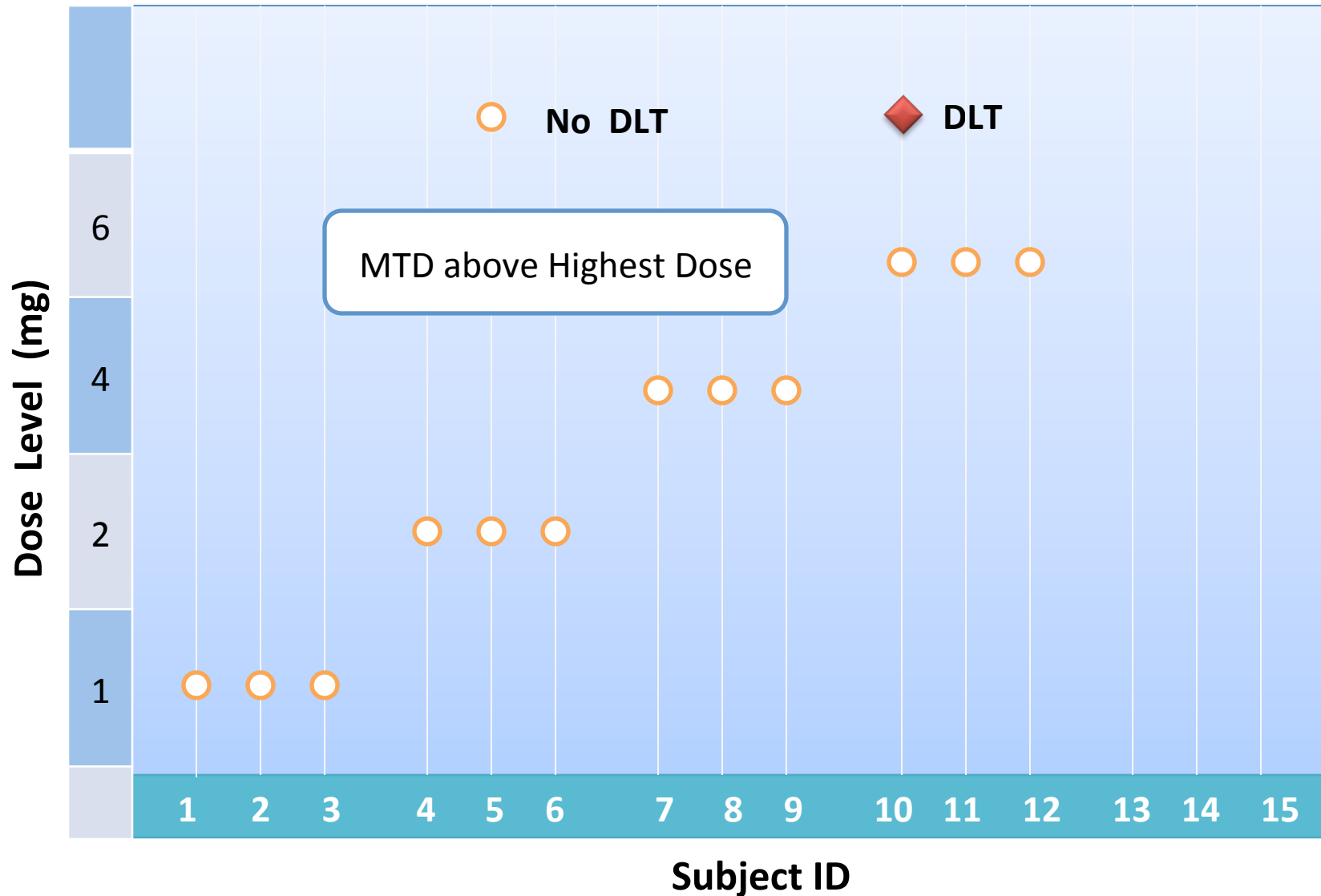
Case Study

Unable to find the MTD

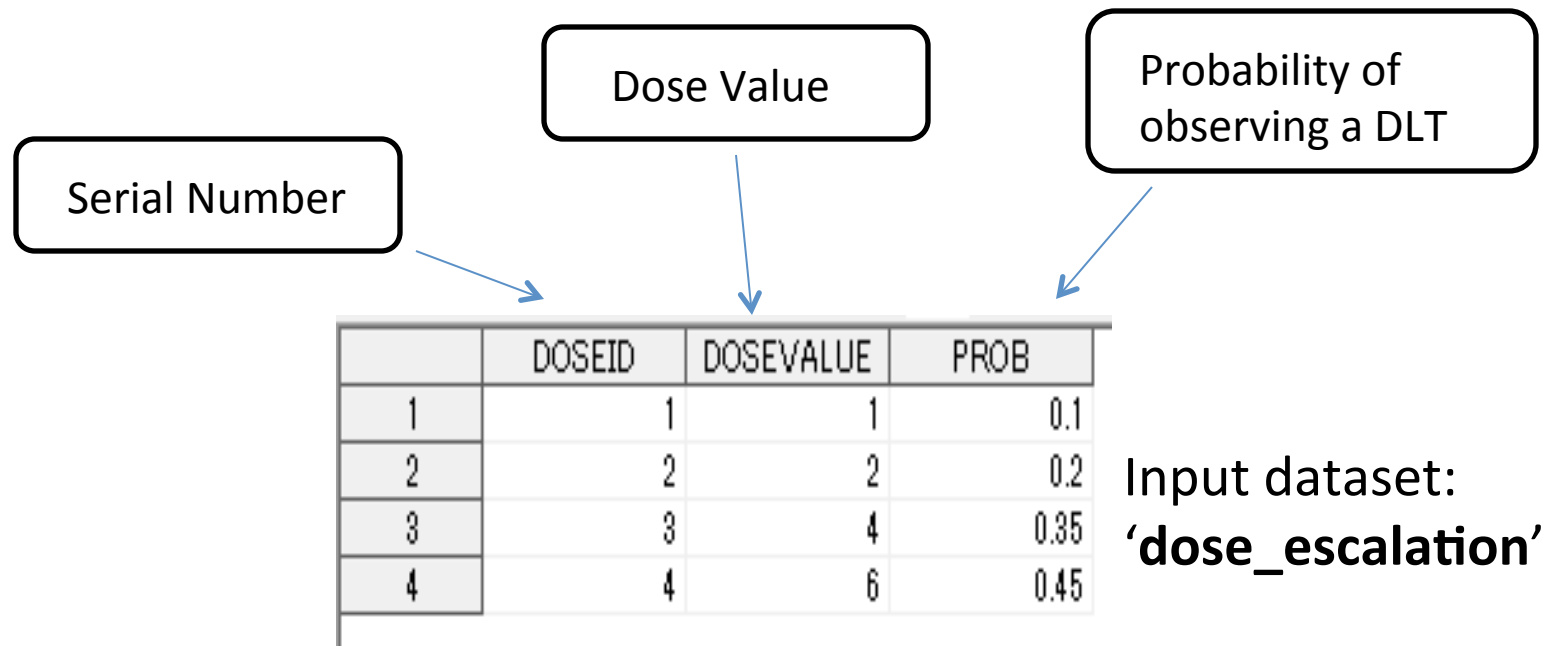


Case Study

Unable to find the MTD



The macro simulates a 3+3 Design



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

Starting Dose

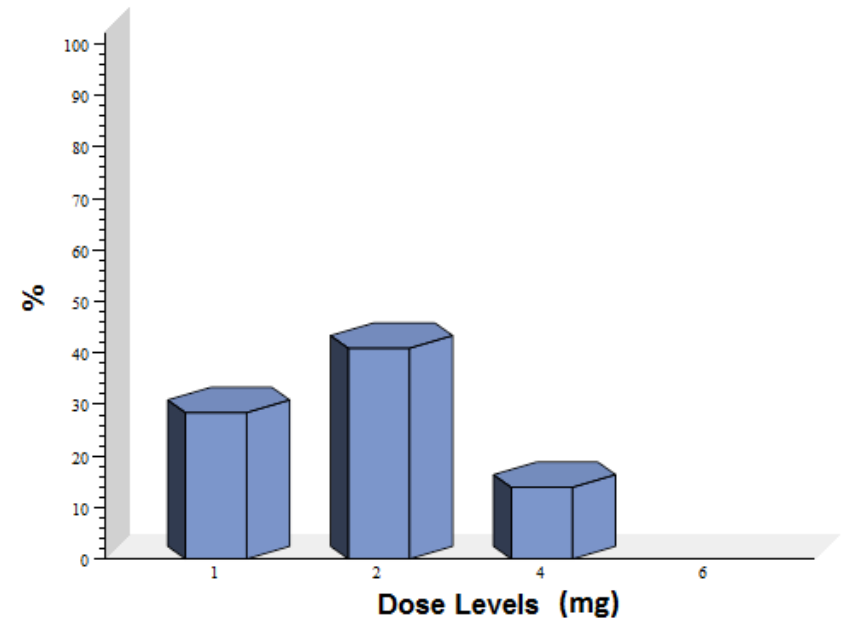
Number of simulations

Maximum Sample Size

Output dataset:
'Simulation_summary'

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

	 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



- 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)

- 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.

- Le Tourneau, Christophe, J. Jack Lee, and Lillian L. Siu. "Dose escalation methods in phase I cancer clinical trials." *Journal of the National Cancer Institute* (2009).
- Storer, Barry E. "Design and analysis of phase I clinical trials." *Biometrics*(1989): 925-937.
- Neuenschwander, Beat, Michael Branson, and Thomas Gsponer. "Critical aspects of the Bayesian approach to phase I cancer trials." *Statistics in medicine* 27.13 (2008): 2420-2439.
- Thall, P. F., and S-J. Lee. "Practical model-based dose-finding in phase I clinical trials: Methods based on toxicity." *International Journal of Gynecological Cancer* 13.3 (2003): 251-261.
- Zohar, Sarah, and Sylvie Chevret. "The continual reassessment method: comparison of Bayesian stopping rules for dose-ranging studies." *Statistics in medicine* 20.19 (2001): 2827-2843.
- O'Quigley, John, Margaret Pepe, and Lloyd Fisher. "Continual reassessment method: a practical design for phase 1 clinical trials in cancer." *Biometrics*(1990): 33-48.
- Case Study : "Tolerability, Immunogenicity and Efficacy of HB-110 Administered by Electroporation in Chronic Hepatitis B Patients." <https://clinicaltrials.gov>

THANK YOU



QUESTIONS