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

Anup Pillai
Cytel, Pune, India

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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

Pre Clinical
- Initial testing done in lab or with animals

Phase - I
- Find the safest dose
- Find most effective way to administer a dose

Phase - II
- Checking for Safety and Effectiveness

Phase - III
- Confirmatory Phase

Phase - IV
- Post Marketing Surveillance

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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

Treat 3 Subjects on Starting Dose $i$

- **0 DLT**
  - 1/6 DLT
    - Escalate to Dose $i+1$
  - > 1/6 DLT
    - De-escalate to Dose $i-1$

- **1 DLT**
  - Enroll 3 more Subjects on Dose $i$

- **> 1 DLT**
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

Subject ID	Dose Level (mg)
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15

No DLT

DLT

MTD

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Case Study

Unable to find the MTD

MTD below Lowest Dose

Subject ID

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15

Dose Level (mg)

1 2 3 4 6

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2015 PhUSE
Unable to find the MTD

MTD above Highest Dose

No DLT

DLT

Subject ID
SAS Macro

The macro simulates a 3+3 Design

Input dataset: ‘dose_escalation’

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

Serial Number
Dose Value
Probability of observing a DLT

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<th>DOSEID</th>
<th>DOSEVALUE</th>
<th>PROB</th>
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Starting Dose
Number of simulations
Maximum Sample Size
Output dataset: ‘Simulation_summary’

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</table>

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


Case Study: “Tolerability, Immunogenicity and Efficacy of HB-110 Administered by Electroporation in Chronic Hepatitis B Patients.” [https://clinicaltrials.gov](https://clinicaltrials.gov)
THANK YOU

QUESTIONS