# Trial Design Module Part 3: Phases of Clinical Trials

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## Agenda

- Phase I
- Phase II
- Phase III
- Phase IV

## Phase I: Goals

- Determine dosing in humans
  - Maximum Tolerated Dose (MTD)
- Assess safety
- Evaluate PKs and PDs
- Explore drug metabolism and drug interactions

## Phase I: Additional Goal(s)

- Also used to:
  - Evaluate new treatment schedule
  - Evaluate new drug combination strategy
  - Evaluate new multi-modality regimen

May provide early evidence of response, but *NOT* primary aim

## Phase I: Subjects

- Healthy volunteers
- Patient volunteers
- Small numbers
  - 15 – 30
  - <100

## Phase I Trial Participant Comparisons

**Healthy Volunteer**

- Illness Free
- Monetary Compensation
- No anticipated personal benefit
- Generally, no more than minimal risk

**Patient**

- Usually end-stage with few if any options for treatment
- "Opportunity" to receive intervention
- Low prospect of personal benefit
- More than minimal risk

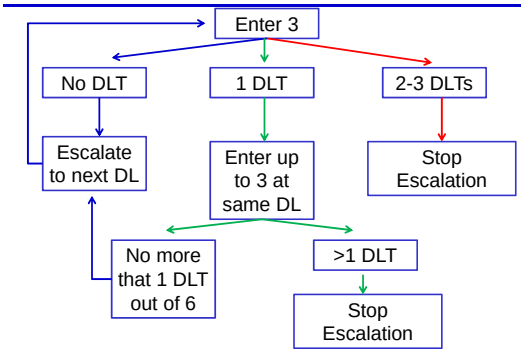
## Phase I: Standard Design

- Open label, non-randomized, dose escalation
- Low starting dose
  - 1/10th the lethal dose (LD10) in the most sensitive species tested = dose at which 10% of the animals die
  - Unlikely to cause serious toxicity
  - Pediatric dose starts at 80% of adult MTD
- 3-6 patients per cohort
- Increase dose gradually
  - Most common scheme is a Modified Fibonacci

## Classic Modified Fibonacci Dose Escalation Scheme

**% Increase Above Preceding Dose:**
Level 1: Starting dose
Level 2: 100% increase from Level 1
Level 3: 67% increase from Level 2
Level 4: 50% increase from Level 3
Level 5: 40% increase from Level 4
Levels 6+: 33% increase from Level 5+

## 3 + 3 Study Design



## Alternate Designs

**Accelerated design**

- 1 subject enrolled per DL until grade 2 toxicity then return to the 3 + 3 design

**OBD**

- Find dose that is considered to safe and have optimal biologic/ immunologic effect (OBD)
- Optimize "biomarker" response within safety constraints

**Intrapatient Dose Escalation**

- Once a DL has been proven "safe" then subjects at lower levels are able to escalate to the "safe" level
- Subject used as own control and can escalated to higher DL if lower level tolerated

## Healthy Volunteer Trial Designs

- Single Ascending Dose (SAD)
- Multiple Ascending Dose (MAD)
- PK/PD
- Food effect studies
- Drug-drug interaction studies
- Q-T interval studies

## Phase I:Endpoints

- Dose Limiting Toxicity (DLT)
  - Define prospectively using rating scale and time limit
- Maximum Tolerated Dose (MTD)
  - Highest dose level at which ≤1/6 patients develop a DLT
- PK/PD

## Phase I: Limitations

- Questionable risks without benefits
- Initial patients may be treated at low doses
- Slow to complete trial
- Toxicity may be influenced by extensive prior therapy
- Inter-patient variability
- MTD definition is imprecise
- Minimal data about cumulative toxicity

## Phase II: Goals

- Provide initial assessment of efficacy or 'clinical activity'
  - Screen out ineffective drugs
  - Identify promising new drugs for further evaluation
- Further define safety and toxicity

## Phase II: Subjects

- ~100 subjects (100-300)
- More homogenous population that is deemed likely to respond based on:
  - phase I data
  - pre-clinical models, and/or
  - mechanisms of action
- Subject needs to have measurable disease
- May limit number of prior treatments

## Phase 2: Designs

- Most common
  - 2 stage design w/ early stopping rule
- Randomized designs
  - Want to explore efficacy
  - Not willing to invest in phase III *(yet)*
  - Want some “control” or “prioritization”

## Phase II: Endpoints

- Response
- Additional safety data

## Phase II: Limitations

- Lack of activity may not be valid
- Have to be able to measure the disease

## Phase III: Goals

- Efficacy compared to standard therapy
  - Activity demonstrated in Phase II study
- Further evaluation of safety

## Phase III: Subjects

- Hundreds to thousands of subjects
- May be front-line or initial therapy
- Well-defined eligibility criteria
- Internal control group
- Multi-institutional participation necessary to reach targeted accrual goals

## Phase III: Standard Design

- Randomized +/- blinding/masking
- Consider stratification

## Phase III: Endpoints

- Efficacy
  - Overall survival
  - Disease-free survival
  - Symptom control
  - Quality of life

## Phase III: Limitations

- Difficult, complex, expensive to conduct
- Large number of patients required
- Incorporation of results into front-line therapy in community is often slow and incomplete

## Phase IV Trial

Follow-up investigation to further evaluate risks, benefits, and optional use of a recently approved drug:

- Different doses or schedules of administration
- Use of the drug in other:
  - Patient populations
  - stages of the disease
- Use of the drug over a longer period of time