Trial Design Module
Part 3: Phases of Clinical Trials

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**

<table>
<thead>
<tr>
<th>Healthy Volunteer</th>
<th>Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Illness Free</td>
<td>Usually end-stage with few if any options for treatment</td>
</tr>
<tr>
<td>Monetary Compensation</td>
<td>“Opportunity” to receive intervention</td>
</tr>
<tr>
<td>No anticipated personal benefit</td>
<td>Low prospect of personal benefit</td>
</tr>
<tr>
<td>Generally, no more than minimal risk</td>
<td>More than minimal risk</td>
</tr>
</tbody>
</table>
Phase I: Standard Design

- Open label, non-randomized, dose escalation
- Low starting dose
  - $1/10^{th}$ 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

- Enter 3
  - No DLT: Escalate to next DL
  - 1 DLT: Enter up to 3 at same DL
  - 2-3 DLTs: Stop Escalation
  - >1 DLT: No more than 1 DLT out of 6
    - >1 DLT: Stop Escalation

Alternate Designs

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

**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

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

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