Clinical Trial Design Guidance

- Clinical Trial: a prospective biomedical or behavioral research study of human subjects that is designed to answer specific questions about biomedical or behavioral interventions. (NIH, PHS398 instructions)
- OHSU Mission Code 54: A study of a drug (device, or diagnostic) where it “…is administered or dispensed to, or used involving, one or more human subjects” and is a “prospective biomedical or behavioral research study of human subjects that is designed to answer specific questions about biomedical...interventions (drugs,...devices, or new ways of using known drugs...or devices).”
- Phases of Clinical Trials
  - For NIH studies: SF424 and PHS398 instructions
  - For drug development: Code of Federal Regulations (CFR): Title 21, Part 312, Section 21 (21CFR312.21)

Regulatory Definitions

- **IND**: Investigational New Drug Application
- **IDE**: Investigational Device Exemption
- **NDA**: New Drug Application
- **PMA**: Premarket Approval
- **BLA**: Biologic License Application
When is an IND/IDE Required?

- The product is investigational (has not been cleared for marketing by the FDA) or;
- The investigation of the product (even if cleared for marketing) poses a significantly increased risk or decreased acceptability of risk
  - Different dose or schedule
  - Different route of administration
  - Different patient population

\[21CFR312.2\]

Approval Process Summary

<table>
<thead>
<tr>
<th>Timeframe</th>
<th>Investigational Product Type</th>
<th>Drug</th>
<th>Biologic</th>
<th>Device (Class III)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start of Development(^1)</td>
<td>IND</td>
<td>IND</td>
<td>IND</td>
<td>IDE</td>
</tr>
<tr>
<td>End of Development(^2)</td>
<td>NDA</td>
<td>BLA</td>
<td>PMA</td>
<td></td>
</tr>
</tbody>
</table>

\(^1\)Before studied in humans

\(^2\)To obtain approval to market

Drug Development Overview\(^1\)

<table>
<thead>
<tr>
<th>Drug Discovery</th>
<th>Drug Development</th>
<th>Market</th>
</tr>
</thead>
<tbody>
<tr>
<td>Task</td>
<td>Task Population</td>
<td>Purpose</td>
</tr>
<tr>
<td>Test</td>
<td>Laboratory and animal studies</td>
<td>Assay, safety and dosage</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Years</th>
<th>0.5</th>
<th>1.5</th>
<th>2</th>
<th>3.5</th>
<th>1.5</th>
<th>1.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test Population</td>
<td>IND, IND, IND</td>
<td>NDA, BLA, PMA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Task</td>
<td>Preclinical Testing</td>
<td>Clinical Trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test</td>
<td>IND, IND, IND</td>
<td>NDA, BLA, PMA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Task</td>
<td>Preclinical Testing</td>
<td>Clinical Trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test</td>
<td>IND, IND, IND</td>
<td>NDA, BLA, PMA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^1\)For Drug Development and Approval Process, © Spilker, PhRMA Publications
Preclinical Testing

- Includes:
  - Basic laboratory testing (test tube and petri dish)
  - Animal testing
- To test:
  - Biological activity
  - Toxicology (carcinogenicity, teratogenicity)
  - Physical chemistry
    - Formulation
    - Interactions
    - Stability

Phase I

- First studies in humans
- To evaluate:
  - Dose
    - Maximum and minimum
    - Schedule/route/regimen
  - Safety
  - Toxicity
  - Other
    - Pharmacokinetics (PK): Distribution and excretion of the drug
    - Pharmacodynamics (PD): Interactions with other agents
Phase I (cont.)

• Subject population:
  – Healthy normal subjects or end-stage patients
  – Men and women
• Sample size: tens
• Typical study design:
  – Cohort dose escalation or multiple dose administration
  – Single center (prolonged observation)
• Usual study duration: ~1 year

Phase II

• To evaluate:
  – Efficacy
  – Target population
  – Safety
  – Dose range
• Utilizes the regimen determined in phase I
• Subject population:
  – Potential target population of patients
  – May be heterogeneous indication

Phase II (cont.)

• Sample size: ~50 - 200 patients
• Typical study design:
  – Controlled (placebo or comparator)
  – Open label or blinded/randomized
  – 2 - 4 study sites
  – Often surrogate endpoints
• Usual study duration: 1 - 2 years
Phase III

- Also called “Pivotal trial”, primary evidence for FDA submission
- Final manufacturing facilities
- To evaluate:
  - Effectiveness
  - Validity of endpoints
  - Long term safety
- Subject population:
  - Target population of patients
  - Single specific indication/study

Phase III (cont.)

- Sample size: hundreds - thousands
- Typical study design:
  - Controlled to standard treatment (placebo if no standard)
  - Randomized, double blinded
  - Multicenter
  - Validated endpoints
- Usual study duration: Usually >2 years

Phase IV

- After approval of the drug/device (post-marketing)
- Maybe required as contingency of approval
- To evaluate:
  - Differential effects in segments of the population
    - Age
    - Gender
    - Race
  - Low incidence toxicities/longterm safety
  - New uses/indications
  - New combinations with other drugs
  - New dosages/regimens
Phase IV (cont.)

- To evaluate (cont.)
  - Marketing issues
    - Comparison with competitor
    - Market priming/testing
    - Market expansion/exposure
  - Drug utilization
    - Cost effectiveness
    - Quality of life
    - Compliance
- May be designed like Phases I-III
- May require an IND if poses an increased risk