Early Phase Trials: Goals and Questions

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- The presenter hereby discloses the following relationships:
  - Berry Consultants, LLC
    - Multiple clients
  - Support from
    - Octapharma AG
    - National Institutes of Health/NINDS
- This presentation will include information on the investigational use of L-carnitine that is not approved for the treatment of sepsis

What is an Early Phase Trial?

- Demonstrating a treatment is adequately effective and safe to warrant clinical adoption generally requires defining the right
  - Population(s)
  - Disease(s)
  - Treatment strategy (e.g., timing, dose, route)
  - Outcome (i.e., responsive to treatment and relevant)
  - Confirmatory trial design
- Early phase trials are designed to reduce uncertainty in these areas, allowing a definitive or successful confirmatory trial to be run

Trial “Phases” in Drugs and Devices

Drugs

- Phase I
  - Bench Work
  - Early Clinical Testing
  - Confirmation of Benefit
  - Analysis & Decisions

Devices

- Phase II
  - Analysis & Decisions

What is an Early Phase Trial?

- General concept: Learn versus confirm
- Learn (e.g., phase I, phase II)
  - Greater flexibility and number of questions/goals
  - Willingness to tolerate higher error rates and sources of bias
  - Not just underpowered confirmatory trials
- Confirm (e.g., phase III)
  - Rigid control of error rates (i.e., type I rate and power)
  - Prespecification and single primary question/outcome
  - Setting for the traditional 1:1 randomized RCT

Early Phase Question: 1

- Can the drug be tolerated?
  - Traditional dose-escalation question
  - Healthy versus diseased population
  - Is the maximum tolerated dose (MTD) of clinical interest
  - Pharmacokinetics versus pharmacodynamics
- Trial Designs:
  - 3+3 (historical interest)
  - Continual reassessment method (CRM)
Early Phase Question: 2

• Can we establish "proof of concept"?
  – Addresses underlying assumptions regarding proposed mechanism of action (e.g., does the drug bind the target receptor, does the drug pass the blood-brain barrier)
  – Assumption is that treatment strategy will not work without this criterion being met (i.e., necessary but not sufficient for success)
  – Trial design: dose ranging/biomarker or assay

Early Phase Question: 3:

• What dose(s) should be investigated further?
  – Potentially useful doses may span a range of several logs
  – Dose selection often requires balance of efficacy and toxicity
  – Common mistake to narrow the dose range under consideration too early
  – Trial design: Dose finding trials with assessment of efficacy and toxicity (e.g., adaptive dose finding trial)

Early Phase Question: 4:

• What outcome(s) should be measured?
  – Consider likelihood of effect on an outcome versus clinical importance (patient centered)
  – Consider practical issues, timing of follow up and difficulty in assessment
  – Reliability and prior validation or use of outcome measures
  – Can consider multiple outcomes, but with risk of false positive result due to "cherry picking"
  – Trial design: Intervention/multiple outcomes

Early Phase Question: 5:

• What disease state(s) should be studied?
  – Consider availability of subjects, confounding factors and treatments, and established outcome measures
  – Common to run multiple phase II trials of the same agent in different diseases
  – Trial design: "Indication finding trial" with multiple diseases enrolled simultaneously to leverage investment in sites and personnel (e.g., using an integrated statistical approach)

Early Phase Question: 6:

• What population should be enrolled?
  – Narrow population:
    • Less variability and easier to interpret results
    • Difficult to enroll required sample size and less clinical relevance
  – Broad population
    • Increased variability, confounding factors
    • Concerns regarding heterogeneity of the treatment effect (HTE) and low power to detect HTE
  – To inform the design of a confirm phase trial, you need to enroll a "confirm-phase" population

Early Phase Question: 7:

• How should a confirmatory study be designed, implemented, and analyzed?
  – Learn-phase trials should be conducted similarly to confirm-phase trials if they are to inform confirm-phase trial design and conduct
  – Same population, treatments, and outcomes
  – Adequate sample size to answer the key questions needed to design confirmatory trial
Early Phase Question 8:

- Should a confirmatory study be conducted at all?
  - We should only run confirmatory trials that have a substantial chance of showing benefit
  - **Key concept**: predictive power—the probability of a positive confirmatory trial, considering all the remaining uncertainties
  - Possible counter-example: trials of treatments to prevent Alzheimer’s disease

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**L-Carnitine and Sepsis**

- **Clinical setting**
  - Adult patients with severe sepsis or shock
  - Phase II, dose-finding trial of L-carnitine to improve end organ function and survival

- **Goals**
  - Identify most promising dose
  - Determine if L-carnitine should be evaluated in a confirmatory, phase III trial
  - Enroll more patients to doses most likely to be beneficial, based on accumulating information

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**Adaptive Trial Structure**

- **Outcome measures**
  - **Proximate**: $\Delta$ SOFA score
  - **Definitive**: Survival to 28 days

- **Structure of trial**
  - 4 arms (0 g, 6 g, 12 g, and 18 g) with dose-response model
  - Maximum sample size of 250 subjects
  - Interim analyses at 40 subjects, then every 12
  - Subjects randomized according to probability that the dose results in the best (negative) $\Delta$ SOFA
  - May be stopped early for futility or success, based on probability that best dose improves SOFA and would be successful in phase III
Operating Characteristics of Proposed Trial Design: Results of Monte Carlo Simulations

<table>
<thead>
<tr>
<th>Assumed Treatment Effects for Simulations</th>
<th>No Effect (Null)</th>
<th>Mild Effect</th>
<th>Strong Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \Delta \text{SOFA Mortality} )</td>
<td></td>
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</tr>
<tr>
<td>Outcome: Control</td>
<td>0</td>
<td>40%</td>
<td>0</td>
</tr>
<tr>
<td>Outcome: 6 g</td>
<td>0</td>
<td>40%</td>
<td>0</td>
</tr>
<tr>
<td>Outcome: 12 g</td>
<td>0</td>
<td>40%</td>
<td>0</td>
</tr>
<tr>
<td>Outcome: 18 g</td>
<td>0</td>
<td>40%</td>
<td>0</td>
</tr>
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Trial Performance

| Probability of Positive Trial | 0.043 (type I error) | 0.911 (power) | 0.999 |
| Probability of Stopping Early | For futility: 0.431  | For futility: 0.001 | For futility: 0.000 |
| Average Req'd Sample Size     | 198.0             | 172.4         | 119.5         |
| Probability of Selecting 18 g | 0.35              | 0.95          | 1.00          |

Average Allocation of Subjects Between Treatment Arms – n per arm (%)

<table>
<thead>
<tr>
<th></th>
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<th>12 g</th>
<th>18 g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>62.7 (32%)</td>
<td>54.1 (33%)</td>
<td>36.5 (11%)</td>
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<tr>
<td>6 g</td>
<td>47.0 (24%)</td>
<td>13.9 (8%)</td>
<td>10.5 (9%)</td>
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<tr>
<td>12 g</td>
<td>38.7 (20%)</td>
<td>31.5 (12%)</td>
<td>12.5 (10%)</td>
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<tr>
<td>18 g</td>
<td>49.6 (25%)</td>
<td>83.0 (48%)</td>
<td>60.0 (50%)</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions

• The goal of an early phase clinical trial is to answer the questions:
  – Should the treatment be further investigated?
  – How should any further trial(s) be designed, conducted, and analyzed?
• The design of an early phase trial must be tailored to allow for
  – Greater uncertainty regarding safety and efficacy
  – Greater uncertainty regarding how best to administer the treatment and measure the effect
  – The need to address multiple trial goals