Early Phase Trials: Goals and Questions

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  – Berry Consultants, LLC
    • Multiple clients
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• This presentation will include information on investigational use of L-carnitine that is not yet 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
Phase II
Phase III

Devices
Bench Work
Early Clinical Testing
Confirmation of Benefit

Analysis & Decisions
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
  - 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 as 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 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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L-Carnitine and Sepsis

**Background**
- L-carnitine is believed to work through reducing multi-organ system failure
- Multi-organ system failure quantified by SOFA score
- Baseline SOFA is key predictor of mortality
- Reduction in SOFA over 48 hours is desired proximate treatment effect
- Reduction in 28-day mortality would be registration endpoint

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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>ΔSOFA Mortality</th>
<th>ΔSOFA Mortality</th>
<th>ΔSOFA Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No Effect</strong> (Null)</td>
<td>0 40%</td>
<td>0 40%</td>
<td>0 40%</td>
</tr>
<tr>
<td><strong>Outcome:</strong> Control</td>
<td>0 40%</td>
<td>0 40%</td>
<td>0 40%</td>
</tr>
<tr>
<td><strong>Outcome:</strong> 6 g</td>
<td>0 40%</td>
<td>0 40%</td>
<td>-1 34%</td>
</tr>
<tr>
<td><strong>Outcome:</strong> 12 g</td>
<td>0 40%</td>
<td>-1 34%</td>
<td>-2 28%</td>
</tr>
<tr>
<td><strong>Outcome:</strong> 18 g</td>
<td>0 40%</td>
<td>-2 28%</td>
<td>-4 19%</td>
</tr>
</tbody>
</table>

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 success: 0.023 For futility: 0.005 For success: 0.679 For futility: 0.001 For success: 0.981
- Average Req’d Sample Size: 198.0 172.4 119.5
- Probability of Selecting 18 g: 0.35 0.99 1.00

Trial Status

- Funded by US National Institutes of Health/National Institute of General Medical Sciences (R01GM103799)
- Led by Alan E. Jones, MD at the University of Mississippi, Department of Emergency Medicine
- Currently enrolling subjects

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