Early Phase Trials: Goals and Questions

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Financial Disclosures

- 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

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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

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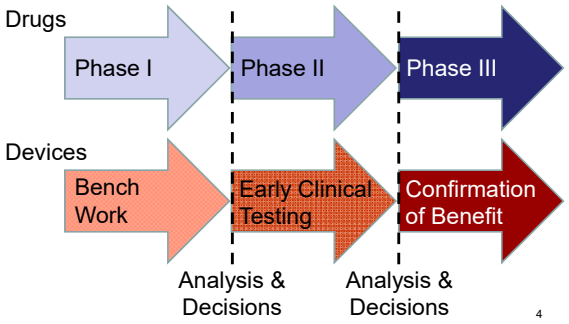
Trial "Phases" in Drugs and Devices



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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

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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)

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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

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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)

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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

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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)

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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

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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

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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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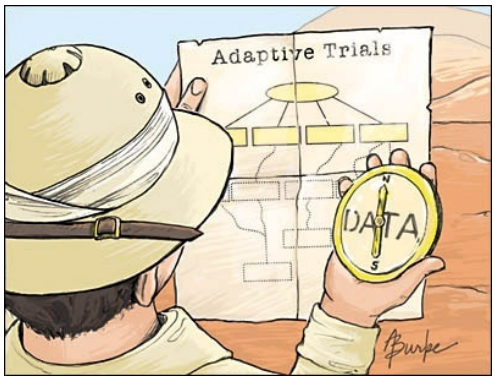

JAMA 2006;296:1955-1957.

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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: Δ 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) Δ SOFA
  - May be stopped early for futility or success, based on probability that best dose improves SOFA and would be successful in phase III

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Operating Characteristics of Proposed Trial Design: Results of Monte Carlo Simulations						
	No Effect (Null)		**Mild Effect**		**Strong Effect**	
Assumed Treatment Effects for Simulations						
	ΔSOFA	Mortality	ΔSOFA	Mortality	ΔSOFA	Mortality
Outcome: Control	0	40%	0	40%	0	40%
Outcome: 6 g	0	40%	0	40%	-1	34%
Outcome: 12 g	0	40%	-1	34%	-2	28%
Outcome: 18 g	0	40%	-2	28%	-4	19%

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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 success: 0.023		For futility: 0.001 For success: 0.679		For futility: 0.000 For success: 0.981	
Average Req'd Sample Size	198.0		172.4		119.5	
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Average Allocation of Subjects Between Treatment Arms – n per arm (%)						
Control	62.7 (32%)		54.1 (31%)		36.5 (31%)	
6 g	47.0 (24%)		13.8 (8%)		10.5 (9%)	
12 g	38.7 (20%)		21.5 (12%)		12.5 (10%)	
18 g	49.6 (25%)		83.0 (48%)		60.0 (50%)	

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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

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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

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