Introduction to Phase II Clinical Trials

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Boston Children's Hospital
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Learning objectives

- Convey the role of phase II clinical trials in research
- Emphasize the importance of statistical design in the conduct of phase II clinical trials
- Provide an understanding of common endpoints and types of designs used in phase II studies

What is “phase II”?

- Phase I: dose finding
- Phase III: definitive comparative study
- Phase II: accomplish everything in between?
  - Feasibility?
  - Pilot?
  - Expansion cohorts?
  - Phase II vs. IIa vs. IIb?
  - “Safety and efficacy”?

Phase II trial goals

- Decide whether further experimentation/study is worthwhile
- Establish activity/efficacy
- Evaluate feasibility of a regimen
- Further evaluate toxicity
- Fine-tune a regimen (dose, schedule, or combination of drugs)

Ideal qualities of a phase II trial

- Provides unbiased and precise information
  - Unambiguous information for a “go / no go” decision
  - Estimates of parameters needed for designing follow-up study
  - Not necessarily definitive
- Robust to things that may/will go wrong
  - Simple is good
- Efficient
  - ‘Quick’ answer

"Design is not just what it looks like or feels like.
Design is how it works."
-Steve Jobs

Determining a phase II design

- What was learned in phase I?
- Do you feel confident with dose, schedule and combination?
- Has this agent been studied in other patient populations?
- What is the mechanism/type of agent?
- Should you use a
  - Binary outcome?
  - Continuous outcome?
  - Time to event outcome?

Accrual

- Sample size is partially determined by accrual rate
- This limits the number of designs you can consider
- Are you studying a relatively rare condition/disease?
- Trade-off between small sample size and multi-center trials
- There is nothing to gain by exaggerating accrual

Early stopping

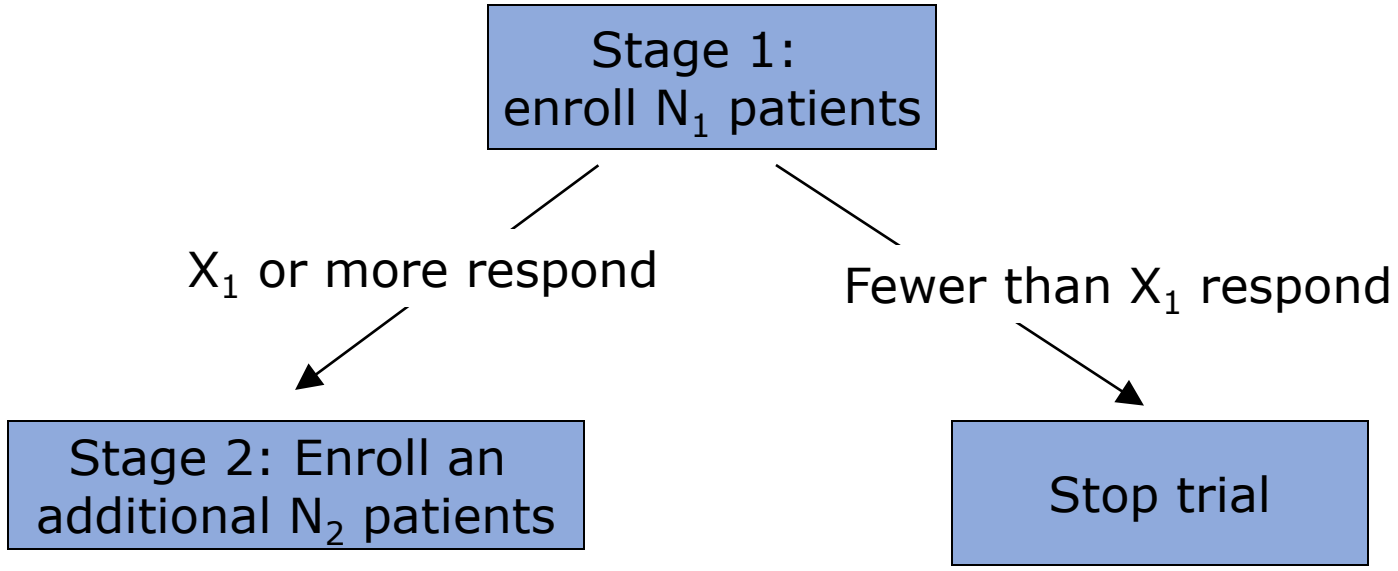
- Accrual and resources
- Unethical to continue enrolling/treating patients on ineffective therapy
- Most phase II studies fail to meet the primary endpoint
- Better to fail early
- Stopping is generally for ‘futility’ only

Design parameters

- Accrual
- Type I error rate
  - One-sided test
  - As high as 0.10
- Power
  - Recommend 90% power
- Null and alternative hypotheses
  - Target a clinically meaningful difference

Single arm trial design

- Outcome is binary (best objective response)
- Allows for early stopping for futility
- Simon Two-Stage Design (Simon, 1989)



Other single arm trial designs

- Binary outcome
  - Single stage design without early stopping
  - Percent alive and progression-free at X months
- Time to event outcome
  - Very challenging to interpret the results without a control arm

Should you randomize?

- Evaluate two regimens concurrently
- Comparison/historical control data not otherwise available
  - Combination drugs vs. single drug
  - New endpoint
- To select one of several experimental arms for further study
  - Pick the winner design
- Looking for small effect or small improvement
- Prelude to a Phase III

Types of randomized designs

- Evaluate 2 novel regimens concurrently
- Evaluating a “new drug” alone and when added to a “backbone” control
  - Looking for activity in a “new drug”
  - Laboratory evidence of synergy with “old drug” or “standard regimen”
- Evaluating >2 regimens
  - Separate trials?
  - Basket/umbrella/platform type of trial?
  - Selection or pick-the-winner design
- Randomized phase II/III design

Advantages and disadvantages

- Advantage
  - More likely to yield unbiased result
  - Subsequently may benefit correlative studies

- Disadvantages
  - Larger study / more than twice as many patients
  - False sense of “unbiasedness”
  - Likely to be over-interpreted
  - Type I error is uncontrolled for multiple comparisons

Choice of primary endpoint

- Impacts the design
  - Largely a function of maturity
  - Sample size
- Select the endpoint that best fits the goals of the study
  - Targeted therapy?
  - Are you evaluating a biomarker?

Types of endpoints

- Objective response by standard criteria
  - RECIST 1.1
  - No censoring, no time component
  - Imprecise measurement
  - DCR is a gamble: stable disease includes patients with a little bit of progression or a little bit of response

Types of endpoints, con't

- Time to event endpoints
  - Power is driven by the number of events
  - Overall survival (OS) is the gold standard, but not feasible to wait for maturity
  - PFS, DFS, RFS, EFS, etc. are all context specific; not all good surrogates for OS
  - Always define events and censoring (never censor deaths)

Other

- Quality research (clinical trials) takes time
- Do not underestimate the amount of time it takes to:
  - Write a detailed and thoughtful protocol
  - Develop case report forms and build the database
  - Complete budgeting/contracts
- No single trial can answer every question

Closing

- Well-designed phase II trials play are an essential in clinical research
- Types of designs and endpoints can vary greatly
- Successful trials are those that can complete accrual and answer a question

Thank you!