

# Why Bother?

- Our primary motivation for investment in adaptive design clinical trials is to *reduce cost of drug development*
  - We want to minimize costs of decisions we come to regret *as new information is learned...* by adapting a trial in a *timely fashion* we may preserve value of investment in it that might otherwise be lost
  - We want to minimize cost of clinical development that is ultimately successful by *making clinical development more efficient*
- Cost is important because *drug development resources are finite*
  - “An adaptive design is not a substitute for an effective drug, in the right population, at the right dose”... but *by reducing costs*, adaptive designs may help us get to this end more often with our finite resources
- *Nothing is ultimately more costly than a bad decision*

# Breakout Session Summaries

A five-minute summary of and comment on topics discussed in each session will be presented by a rapporteur

## A. Procedural and DMC Issues in an Adaptive Paradigm

Steve Snapinn, Amgen

## B. Considerations for Adaptation in Confirmatory Trials

Robert Meyer, FDA

## C. Seamless Phase II/III Designs

David Ross, FDA → Dept. of Veterans Affairs

## D. Dose Finding

Stella Machado, FDA

# Determinants of Cost

- Cost usually increases with total number of patients studied
  - Want to generate information necessary for support of decisions with as few patients as possible
- Two separate trials usually cost more than one trial, even if the total number of patients is the same
- Cost savings are possible with early stopping
- Cost of interim analyses and increased sample size necessary to maintain overall Type 1 error rate must be considered along with probability of saving money by stopping early
  - Rapid access to and frequent looks at data can be costly
- Time → loss of patent protection/market exclusivity
- Complexity of conduct, analysis, interpretation, review → increased time and/or cost
- Some “costs” are difficult to measure
  - Giving some patients in studies less than the best possible treatment
  - Delaying availability to general public of valuable new treatments

# Alternatives

1. Two separate trials with minimal “white space” between them (second trial independent of first)
2. “Restart” of a single trial after adaptation (single protocol, final analysis to only include data after restart)
3. *Single trial with adaptive design* (final analysis to include data before and after adaptation)

## Some key issues identified:

- Information necessary to sensibly support adaptation decisions
- Cost and time to complete the trial(s)
- Probability of false positive results (from 1 trial vs. from 2 trials)
- Probability of detecting treatment value (assuming it is present)
- Timing/number/nature of regulatory agency, ethical review board, and data monitoring committee interactions necessary
- “Message” delivered to external observers by adaptation, start of second trial, or restart of trial may change expectation of treatment effect and thus impact results observed subsequently
- Value added by versus cost of the white space