

# ADAPTIVE DESIGNS AND SMALL CLINICAL TRIALS

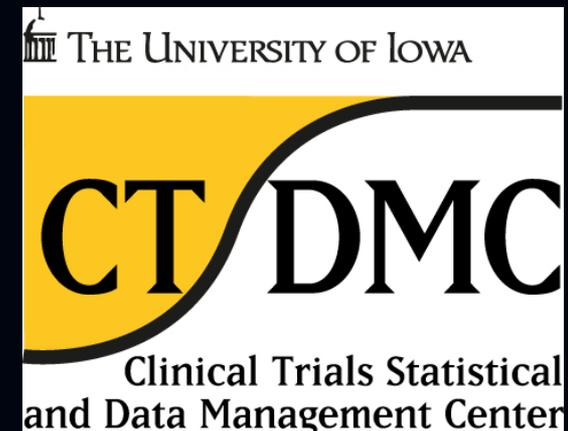
**Christopher S. Coffey**

**Professor, Department of Biostatistics**

**Director, Clinical Trials Statistical and Data**

**Management Center**

**University of Iowa**



# OUTLINE

In this lecture, we will:

- I. Discuss the importance of adequate study planning for small clinical trials
- II. Understand what is meant by an adaptive design
- III. Understand differences among various types of adaptive designs – with special emphasis on those related to small clinical trials

# OVERVIEW

The wonderful land of Asymptopia:



# OVERVIEW

Small clinical trials present unique challenges.

Small clinical trials are more prone to variability and may only be adequately powered to detect large intervention effects.

As a consequence, the importance of adequate study planning is magnified in small clinical trials.

It is often the case that more time is required during the study planning for small clinical trials.

Critically important to have a true collaboration between clinicians and statisticians!

# OVERVIEW

To compute the required sample size for addressing the primary question of interest, we need to specify:

- Target power
- The significance level –  $\alpha$
- A clinically important difference that we wish to detect –  $\delta$
- Any additional nuisance parameters (variance, control group event rate, etc.)

# OVERVIEW

Small changes in design parameters may yield large changes in power.

In general, one can increase the sample size to achieve a greater level of power.

However, this may not be possible in small clinical trials and/or studies of rare diseases.

In such instances, it is vitally important to minimize the variability of the treatment difference of interest.

Novel designs also have great appeal in such settings.

# ADAPTIVE DESIGNS

There may be limited information to guide initial choices for the design of a study.

Since more knowledge will accrue as the study progresses, adaptive designs allow these elements to be reviewed during the trial.

An *adaptive design* allows for changing or modifying the characteristics of a trial based on cumulative information.

# ADAPTIVE DESIGNS

Recently, there has been considerable research on adaptive designs (ADs).

The rapid proliferation of interest in adaptive designs and inconsistent use of terminology has created confusion about similarities and differences among the various techniques.

For example, the definition of an “adaptive design” itself is a common source of confusion.

# ADAPTIVE DESIGNS

PhRMA Working Group on Adaptive Designs (2006):

“By adaptive design we refer to a clinical study design that uses accumulating data to modify aspects of the study as it continues, without undermining the validity and integrity of the trial.”

“...changes are made by design, and not on an ad hoc basis”

“...not a remedy for inadequate planning.”

# ADAPTIVE DESIGNS

Infinite number of adaptive design possibilities:

- Many aspects of the study can be changed:
  - dosing
  - final test statistic
  - primary endpoint
  - number of treatment arms
  - Number of interim looks  
inferiority
  - sample size
  - treatment allocation ratio
  - inclusion/exclusion criteria
  - randomization procedure
  - goal: superiority to non-
- In all cases, objectives should be clearly defined and the operating characteristics should be well understood (i.e., impact on type I error rate).

# ADAPTIVE DESIGNS

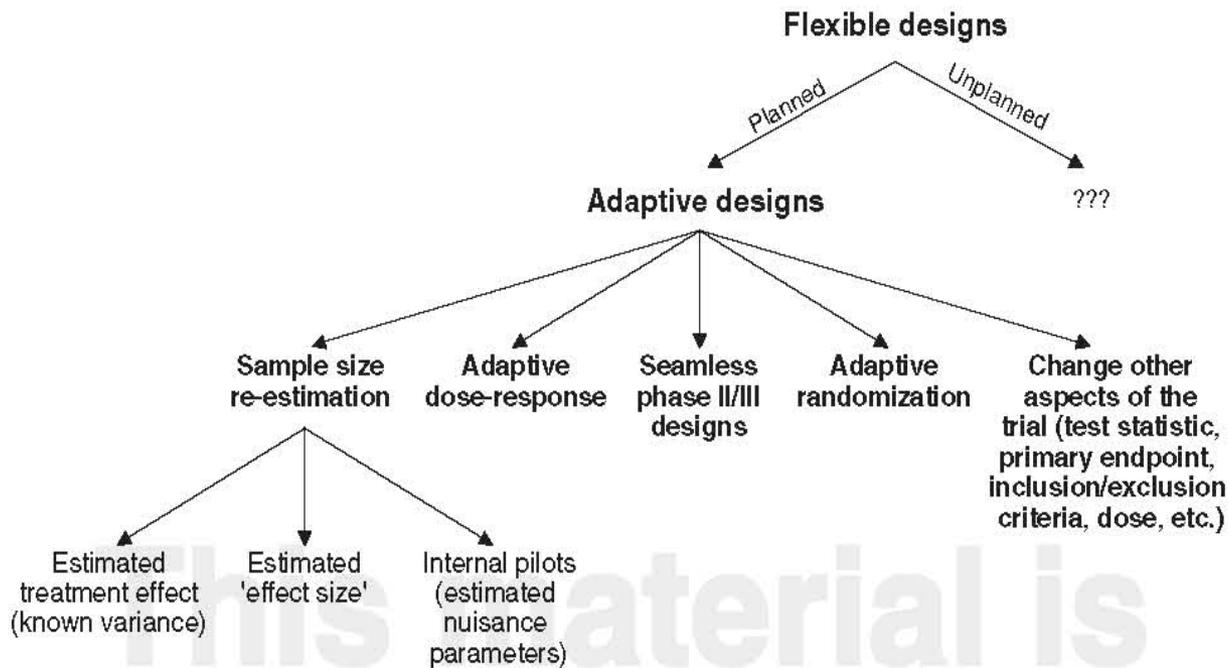


Fig. 1. Summary of different types of adaptive designs for clinical trials.

**Source: Coffey CS and Kairalla JA (2008). Adaptive Designs: Progress and Challenges. Drugs in R&D, 9(4): 229-242.**

# GROUP SEQUENTIAL DESIGNS

Group sequential designs are useful for monitoring ongoing study data.

Given this definition of an AD, a group sequential design is an AD that allows for premature termination of a trial due to efficacy or futility – based on the results of an interim analysis.

Hence, group sequential designs are one of the most commonly used ADs in clinical trials.

# GROUP SEQUENTIAL DESIGNS

Several approaches have been proposed to adjust for the repeated application of significance tests and control the overall study type 1 error rate.

***Many are based on large sample theory.***

Accordingly, variance estimates are often treated as known quantities during analysis and asymptotically correct Z-distributions (i.e, Z) are used for critical value calculation.

For small clinical trials, these distributions become increasingly inaccurate and may lead to an inflation in the type I error rate.

# GROUP SEQUENTIAL DESIGNS

Pocock (17) suggested a simple, easy approach for small clinical trials.

Use the significance level of Gaussian derived critical values using  $\alpha$ -spending functions and sample size to compute critical values from a t-distribution.

For example, if the O-F stopping rule is to stop if  $p < 0.002$  ( $Z_{\text{crit}} = 2.88$ ) with  $n_1 = 100$ , then define the critical value as:

$$t_{\text{crit}} = t^1(1-0.002, 99) = 2.95$$

# ADAPTIVE DOSE FINDING

Adaptive dose finding methods:

- Offer more efficient ways to learn about dose response
- Provide more information on dose response earlier in development
- Guide decision making on whether to continue program and, if so, which dose to select for further development
- Aim to increase probability of technical success by taking correct choice of dose forward for further study

# ADAPTIVE DOSE FINDING

## Continual Reassessment Method (CRM):

- Originated as a Bayesian method for phase I cancer trials of cytotoxic agents.
- Assumes that probabilities of both efficacy and toxicity increase with increasing dose
- Assumes a particular model (such as logistic function)
- Assignment of doses converges to the MTD.
- See Garrett-Moyer (2006) for an excellent tutorial.

# ADAPTIVE DOSE FINDING

Steps for implementing CRM:

- 1) Begin with assumed a priori dose-toxicity curve and chosen target toxicity rate
- 2) Assign first patient dose most likely to be associated with target toxicity level.
- 3) After observing response for first patient, estimated dose-toxicity curve is refit
  - Posterior distribution of model is updated
  - Updated curve shifted slightly up or down depending on whether patient experienced a dose-limiting toxicity

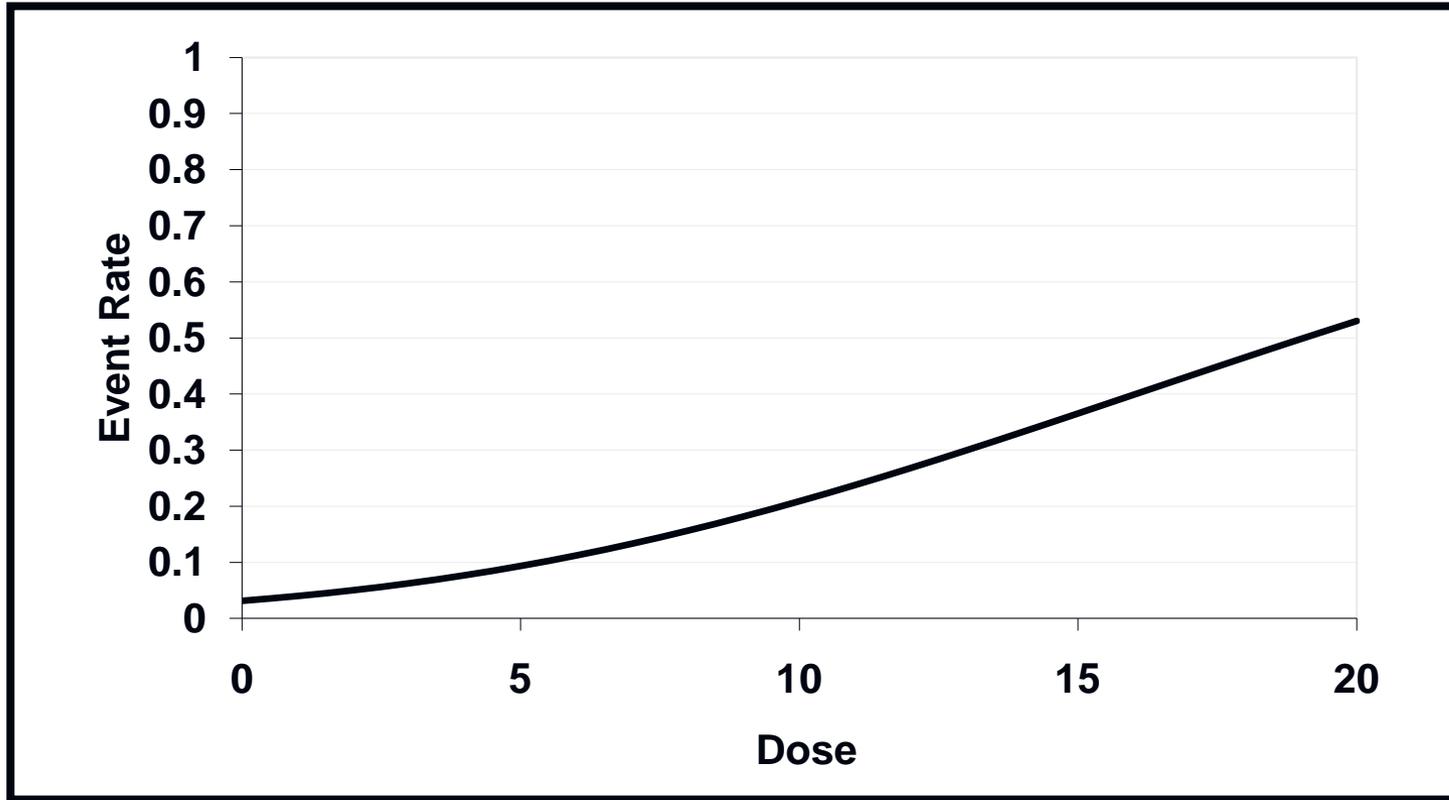
# ADAPTIVE DOSE FINDING

Steps for implementing CRM (cont.):

- 4) Next patient assigned dose closest to target toxicity level based on updated curve.
- 5) Continue process until some pre-defined level of certainty achieved or pre-defined stopping criteria met.
- 6) Once stopping criteria achieved, final dose is selected as the MTD.

# ADAPTIVE DOSE FINDING

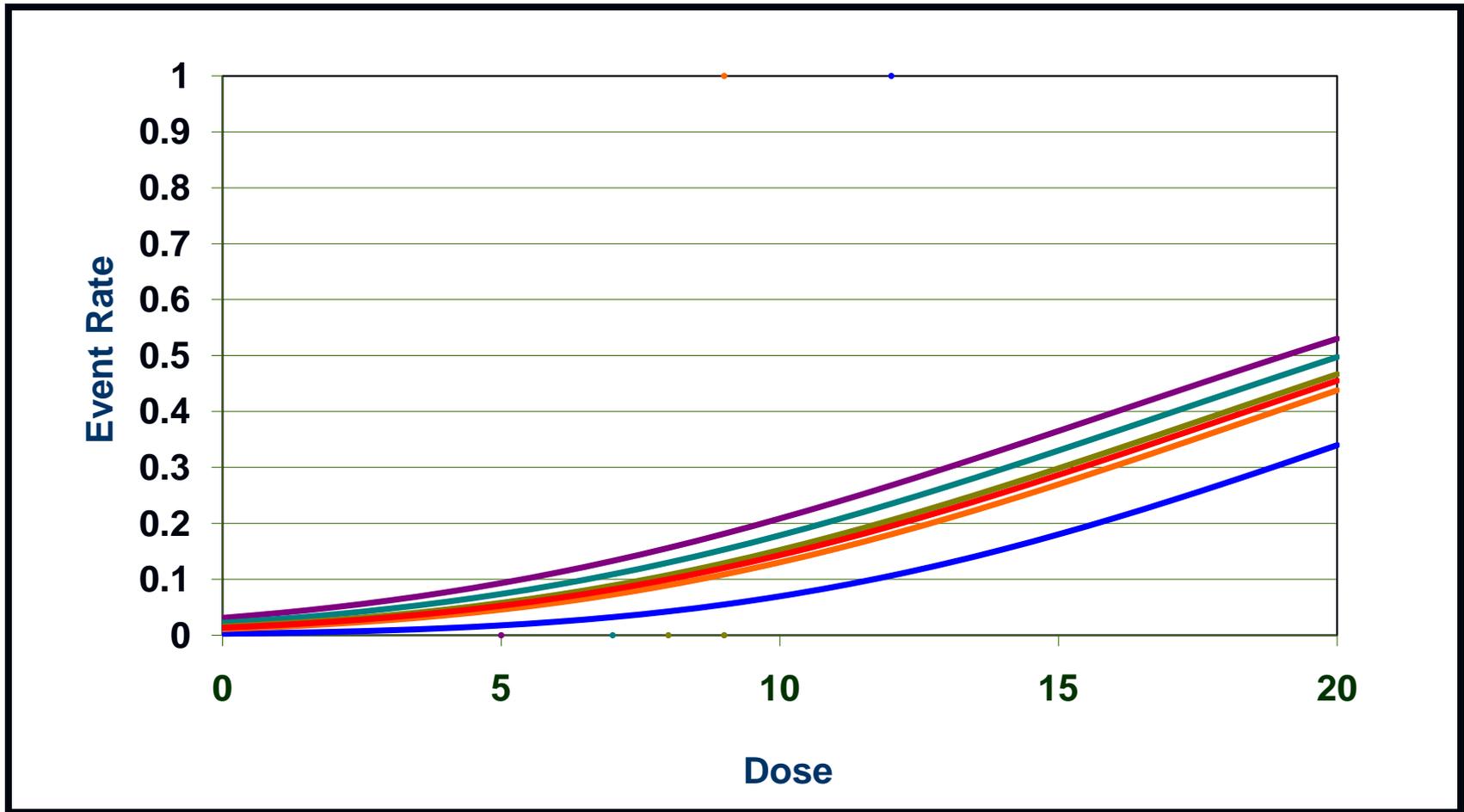
For example, consider the following curve:



If target level of toxicity is 10%, then dose level 5 would be the optimal starting dose.

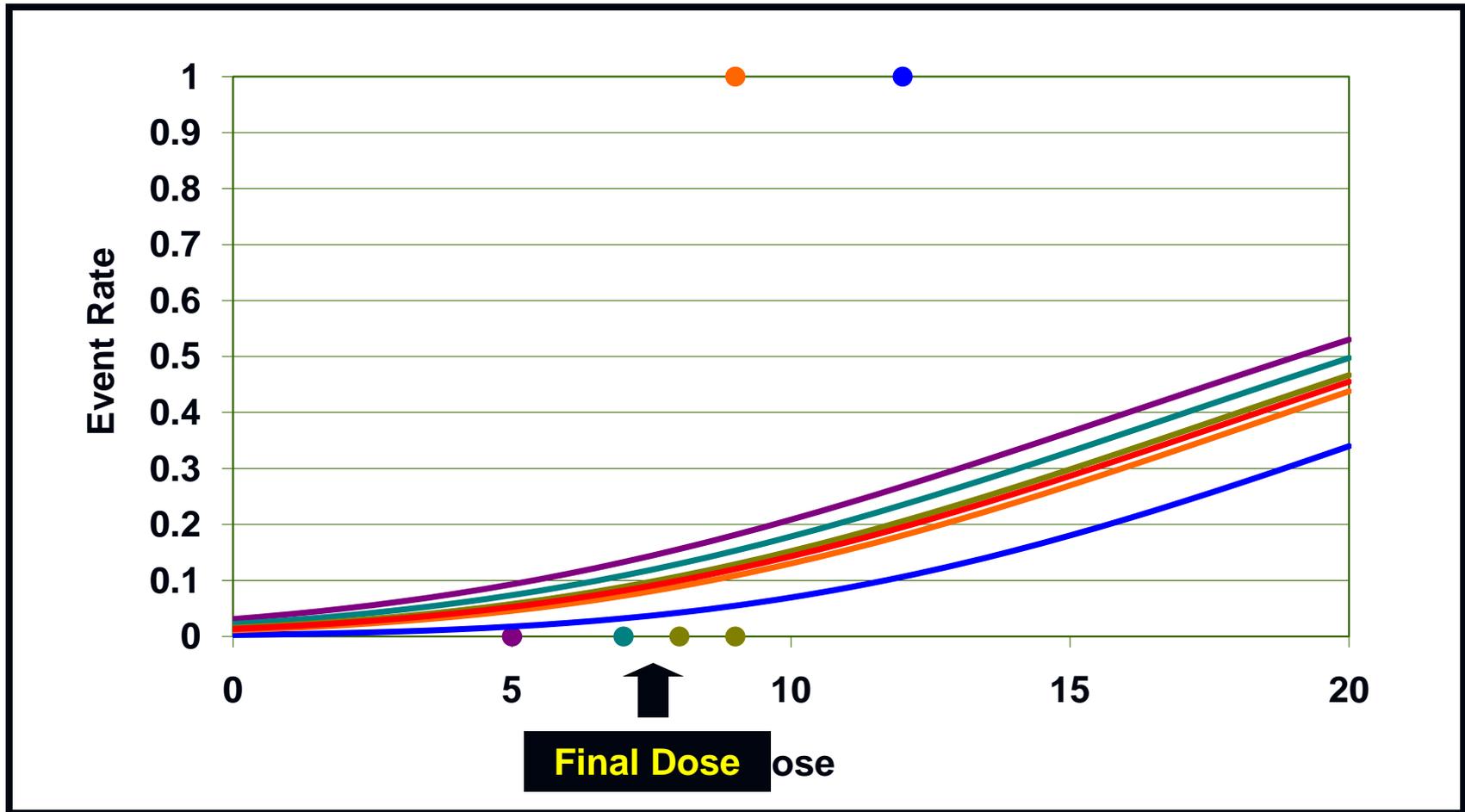
# ADAPTIVE DOSE FINDING

An example of how the CRM might work:



# ADAPTIVE DOSE FINDING

An example of how the CRM might work:



# ADAPTIVE DOSE FINDING

Several modified CRM approaches have been developed to address concerns with original CRM:

- Always start at lowest dose level under consideration
- Enroll 2-3 patients in each cohort
- Any given dose escalation cannot increase by more than one level.

# ADAPTIVE RANDOMIZATION

An *adaptive randomization* design allows modification of randomization schedules for assigning patients to treatment groups during the conduct of the trial.

With *response adaptive randomization*, allocation probability is based on responses observed in previous patients.

With *covariate adaptive randomization*, allocation probability is chosen to reduce covariate imbalance between groups.

# BIOMARKER ADAPTIVE RANDOMIZATION

A *biomarker adaptive design* allows for adaptations based on short-term biomarkers that are thought to inform the treatment effect on a clinical endpoint.

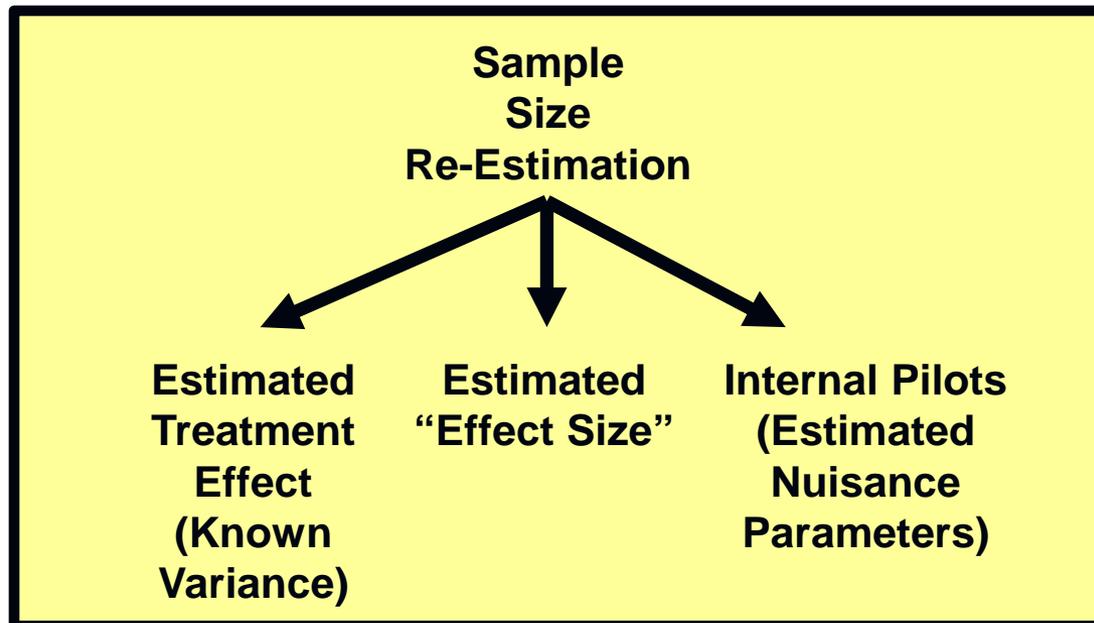
In such designs, biomarkers may be used at an interim analysis to assist in decision making.

The final analysis may still be based on the gold standard endpoint.

# SAMPLE SIZE RE-ESTIMATION

A *sample size re-estimation* (SSR) design refers to an adaptive design that allows for adjustment of sample size based on a review of the interim data.

Historically, a great deal of controversy has been focused around a particular type of SSR design:



# SAMPLE SIZE RE-ESTIMATION

*Internal pilot* (IP) designs based modifications only on re-estimated nuisance parameters.

IP designs can be used in large RCT's to re-assess key nuisance parameters and make appropriate modifications with little cost in terms of inflated type I error rate!

This is not true with small clinical trials and methods are required to adjust for possible bias.

(Stein, 1945; Zucker et al, 1999, Proschan & Wittes, 2000, Kieser & Friede, 2000; Coffey & Muller, 2001)

# ADAPTIVE DESIGNS

Group Sequential Methods vs. Internal Pilots:

Group Sequential Methods

- Protect against observing a larger or smaller than expected effect during the course of a study

Internal Pilots

- Protect against mis-specification of nuisance parameters at the design stage

An information based monitoring approach allows an internal pilot to be used within a group sequential framework.

# ADAPTIVE DESIGNS

Mehta & Tsiatis (2001) and Tsiatis (2006) proposed an asymptotically correct method for simultaneous use of group sequential and internal pilot designs in RCT's.

However, asymptotic theory may not control type I error rate in small clinical trials.

Kairalla et al (2010) provided exact theory and methods for single degree of freedom tests.

Current research seeks to utilize this theory to control potential error inflation in small clinical trials.

# ADAPTIVE SEAMLESS DESIGNS

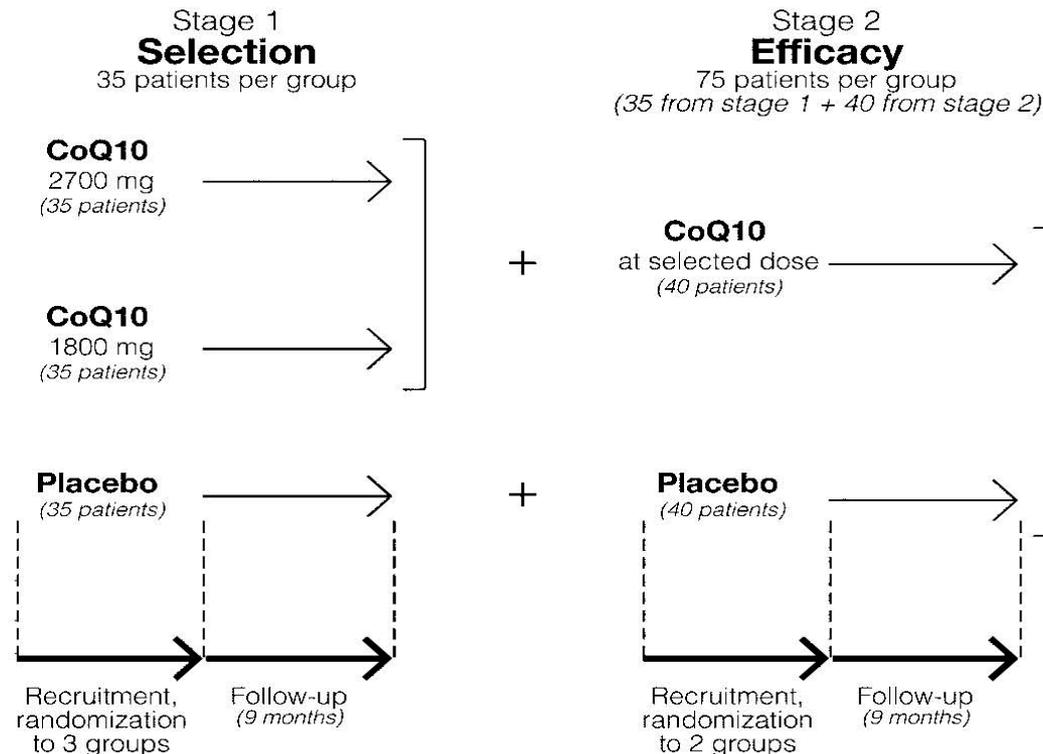
A *seamless design* combines objectives traditionally addressed in separate trials into a single trial.

An *adaptive seamless design* combines trials and uses data from patients enrolled before and after the adaptation for the final analysis.

Most interest to date has been with a seamless transition between phase IIb (learning) and III (confirming).

# ADAPTIVE SEAMLESS DESIGNS

However, there are also opportunities for seamless designs in early development (phase I/IIa).



*Figure. Two-stage phase II design of the Clinical Trial of High Dose Coenzyme Q10 in ALS (QALS study; total: 185 patients, 105 in stage 1 and 80 in stage 2).*

# ADAPTIVE SEAMLESS DESIGNS

Adaptive seamless designs have the potential to improve the drug development process by reducing the timelines for approval.

Statistical methods must account for the fact that data from the second stage are combined with relevant data from stage one in final analysis.

Hence, extra planning is necessary when implementing an adaptive seamless design protocol.

The potential benefits should be carefully weighed against the challenges of such designs.

# ADAPTIVE SEAMLESS DESIGNS

Furthermore, at the end of each phase in a traditional approach, the analysis and interpretations are mainly performed by the sponsor.

As a consequence, the “go” or “no go” decision is fully made by the sponsor unless there is a safety concern.

However, with seamless designs, there is a concern that the decisions made have the potential to convey knowledge to observers based on actions taken based on the interim results.

# ADAPTIVE SEAMLESS DESIGNS

To alleviate the concern, the DSMB may play an important role in the decision-making process between phases.

As a consequence, the roles and responsibilities of the DSMB are beginning to become more complex.

# SUMMARY

An appropriate study design has sufficient sample size, adequate power, and proper control of bias to allow a meaningful interpretation of the results.

Although small clinical trials pose important limitations, the above issues cannot be ignored.

The majority of methods research for clinical trials / adaptive designs is based on large sample theory.

Additional research into innovative designs for small clinical trials is needed.

See FDA draft guidelines released earlier this year for further information.