Short Course: Adaptive Clinical Trials

Presented at the 2011 Annual Meeting
of the Society for Clinical Trials
Vancouver, Canada

Roger J. Lewis, MD, PhD
Department of Emergency Medicine
Harbor-UCLA Medical Center
David Geffen School of Medicine at UCLA
Los Angeles Biomedical Research Institute
Berry Consultants, LLC

Financial Disclosures

- Berry Consultants, LLC
  - Multiple clients
- U01 Support from
  - National Institutes of Health
  - Food and Drug Administration
- AspenBio Pharma
- Cell>Point, LLC
- Octapharma USA
- Octapharma AG

Outline

- The “philosophy” of adaptive clinical trials
  - Planned change is good!
- Categories of adaptive trial designs
- Specific adaptive strategies
- Implementation/Logistics
- Data and Safety Monitoring Boards
- Acceptability to key stakeholders

“Philosophy” of Adaptive Trials

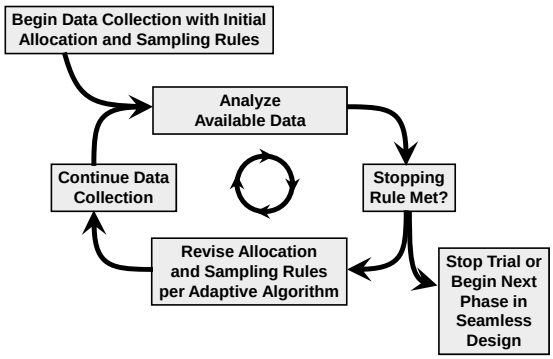
- Clarity of goals
  - E.g., Proof of concept vs identification of dose to carry forward vs confirmation of benefit
- Frequent “looks” at the data and data-driven modification of the trial
- Adaptive “by design”
- Extensive use of simulation to “fine tune” key trial characteristics

JAMA 2006;296:1955-1957.

Adaptation: Definition

- Making planned, well-defined changes in key clinical trial design parameters, during trial execution based on data from that trial, to achieve goals of validity, scientific efficiency, and safety
  - Planned: Possible adaptations defined *a priori*
  - Well-defined: Criteria for adapting defined
  - Key parameters: *Not* minor inclusion or exclusion criteria, routine amendments, etc.
  - Validity: Reliable statistical inference

The Adaptive Process



Historical Context

- Historically, obtaining results that were "reliable and valid" required fixed study designs
- Allowed the determination of theoretical error rates
- Fundamental characteristic of the "culture" of biostatistics and clinical trial methodology

Why are Study Designs Fixed?

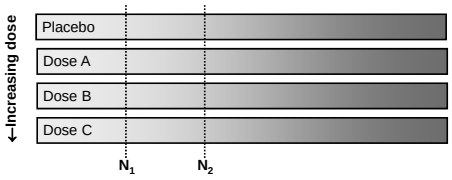
- It's easiest to calculate type I error rates if the design parameters of the trial are all constant
- There are some other reasons:
  - Results obtained using "Standard approaches" are generally considered valid
  - Logistically simpler to execute
  - Fixed designs are less sensitive to "drift" in the characteristics of subjects over time

Type of Adaptive Rules

- **Allocation Rule**: how subjects will be allocated to available arms
- **Sampling Rule**: how many subjects will be sampled at next stage
- **Stopping Rule**: when to stop the trial (for efficacy, harm, futility)
- **Decision Rule**: decision and interim decisions pertaining to design change not covered by the previous three rules

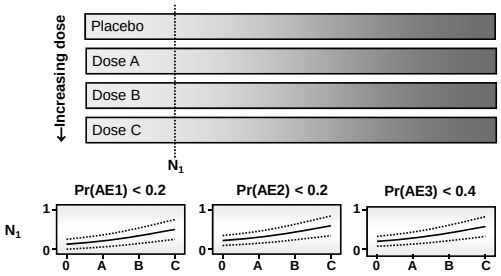
Adapted from Vlad Dragalin

Example



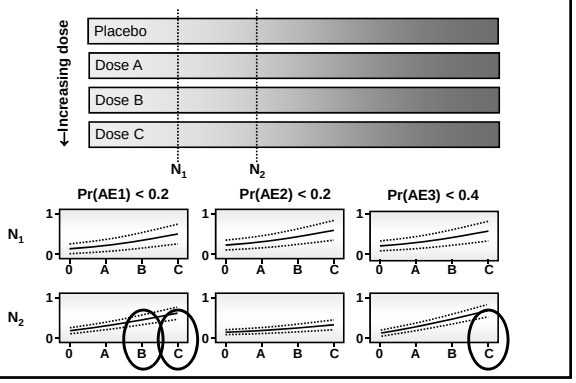
- **Rule:**
  Drop a dose if rate of AE1, AE2, or AE3 appears to be above the tolerable limit at either N_1 or N_2 based on lower limit of model-based 80% CI:
- **Limits:**
  Pr(AE1) < 0.2
  Pr(AE2) < 0.2
  Pr(AE3) < 0.4

Example

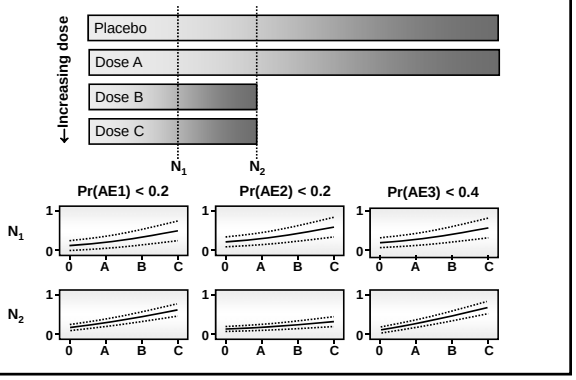


No dose meets criteria for early termination so all will be continued until N_2.

Example

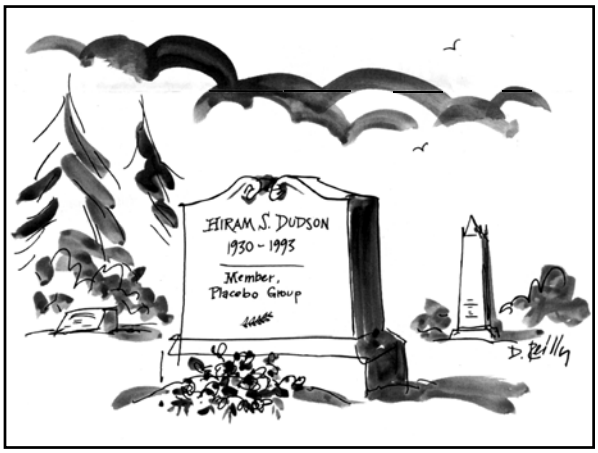


Example



Example

- Simulations, conducted under a wide range of assumptions regarding the rates of AE1, AE2, and AE3, used to verify:
  - Ability of design to reliably terminate poorly tolerated arms
  - Ability of design to reliably retain well-tolerated arms
- Learn phase (phase II dose finding) study
  - Control of type I error rate for efficacy based on taking ≤ 2 active arms forward



When is Adaptation Most Valuable?

- Outcomes or biomarkers available rapidly relative to time required for entire trial
- Substantial morbidity, risks, costs
- Large uncertainty regarding relative efficacy, adverse event rates, etc.
- Logistically practical
- Able to secure buy-in of stakeholders

Why Not Adapt?

- Determining traditional type I and type II error rates is more difficult
  - Usually need to use simulation
- Statistical training issues
  - Most statisticians have never designed or analyzed an adaptive trial
- Logistical Issues
  - Data availability
  - Centralized randomization
  - Drug supply

Categories of Adaptive Trials

- Can be classified based on adaptive component(s)
  - Allocation rule **Response-adaptive dose finding**
  - Sampling rule **Sample size re-estimation**
  - Stopping rule **Group sequential trial**
  - Decision rule **Seamless phase II/III**
- Goal and place in drug development
  - Learn versus confirm
  - Proof of concept, dose finding, seamless phase II/III

Categories of Adaptive Trials

- Information driving adaptation
  - Adaptive
    - Covariates
    - Variance **Sample size re-estimation**
  - Response adaptive
    - Primary endpoint
    - Biomarker **Response-adaptive dose finding**
    - Safety outcomes

Some (Bayesian) Adaptive Strategies

- Frequent interim analyses
- Explicit longitudinal modeling of the relationship between proximate endpoints and the primary endpoint of the trial
- Response-adaptive randomization to efficiently address one or more trial goals
- Explicit decision rules based on predictive probabilities at each interim analysis
- Dose-response modeling
- Extensive simulations of trial performance

Frequent Interim Analyses

- **Frequent interim analyses** based on Markov-chain Monte Carlo (MCMC) estimates of Bayesian posterior probability distributions, with multiple imputation and estimation of unknown trial parameters and patient outcomes.
- Typically quantify
  - Evidence of treatment efficacy
  - Trial futility/predictive probability of success
  - Safety and rates of adverse events

Longitudinal Modeling

- Explicit **longitudinal modeling** of the relationship between proximate endpoints and the primary (generally longer term) endpoint of the trial to better inform interim decision making, based on the data accumulating within the trial and without assuming any particular relationship at the beginning of the trial.
- Used to learn about, and utilize, the relationship between proximate and final endpoints
- Frequently misunderstood as “making assumptions” or using “biomarkers”

Response-adaptive Randomization

- **Response-adaptive randomization** to improve important trial characteristics
- May be used to address one or more of:
  - To improve subject outcomes by preferentially randomizing patients to the better performing arm
  - To improve the efficiency of estimation by preferentially assigning patients to doses in a manner that increases statistical efficiency
  - To improve the efficiency in addressing multiple hypotheses by randomizing patients in a way that emphasizes sequential goals
  - Includes arm dropping

Decision Rules/Predictive Probabilities

- Explicit **decision rules based on predictive probabilities** at each interim analysis to define when to stop for futility, early success, etc.
- Examples
  - May define success or futility based on the predictive probability of success if trial is stopped and all patients followed to completion
  - May define success or futility based on the predictive probability of success of a **subsequent** phase III trial
  - May combine probabilities logically: probability that the active agent is **both** superior to a control arm and non-inferior to an active comparator
  - Design "transitions": e.g., phase II to phase III

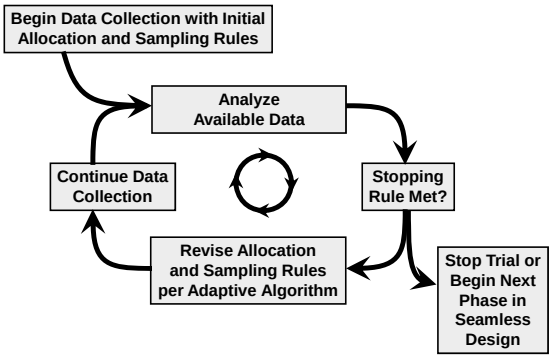
Dose-response Modeling

- **Dose-response modeling**, when applicable, so that information from all patients informs the estimate of the treatment effect at all doses—this improves the reliability of interim decision making and improves accuracy in the updating of interim randomization proportions.
- Examples
  - Logistic dose-response model: assumes monotonicity
  - Normal dynamic linear model (NDLM): borrows information from adjacent doses but doesn't assume a particular shape of the relationship

Extensive Simulations

- **Extensive simulations of trial performance** to ensure that the type I error rate, power and accuracy in estimation of treatment effect(s), the rates of adverse events, or dose finding are well defined and acceptable, across a very wide range of possible true treatment effect sizes, dose-response relationships, and population characteristics.
- Often end up exploring and understanding the performance characteristics across a range of null hypotheses much broader than with traditional approaches

The Adaptive Process



Components of an Adaptive Trial

Management

Adaptive Machinery

Logistics

Drug Supply | Randomization System | CRO/Data Management

Clinical

Site 1 | Site 2 | • • • | Site n

Components of an Adaptive Trial

Management

Adaptive Machinery

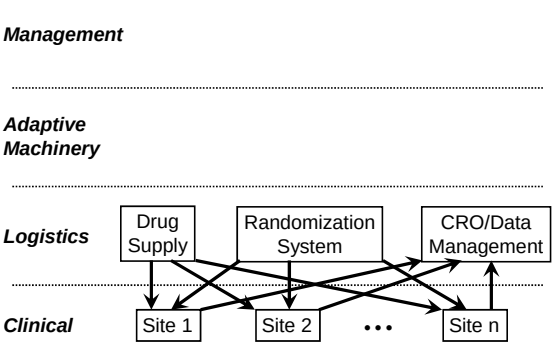
Logistics

Drug Supply | Randomization System | CRO/Data Management

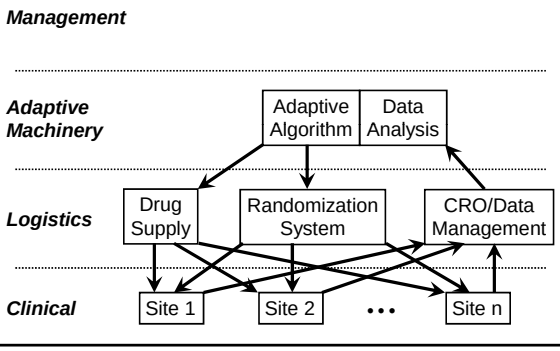
Clinical

Site 1 | Site 2 | • • • | Site n

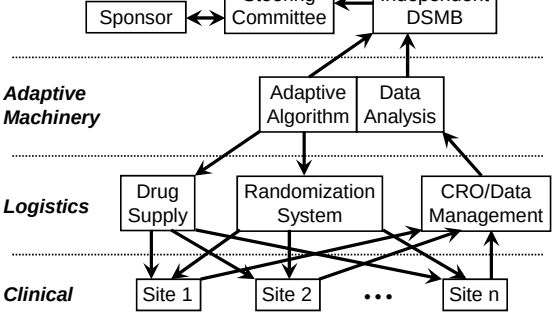
Components of an Adaptive Trial



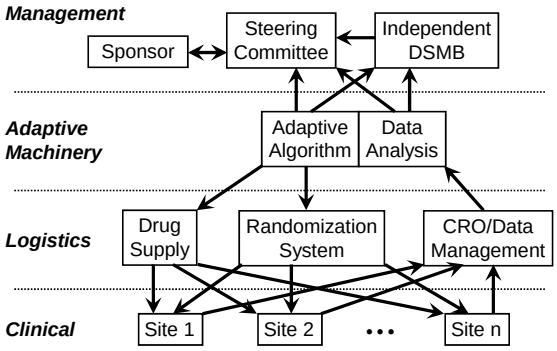
Components of an Adaptive Trial



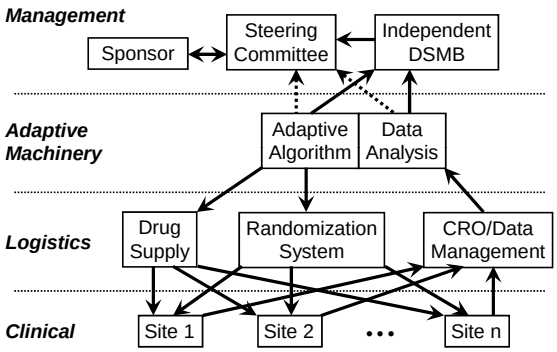
Components of an Adaptive Trial



Components of an Adaptive Trial



Components of an Adaptive Trial



Data and Safety Monitoring Boards

- Purpose
  - To ensure continued safety, validity, feasibility, and integrity of the clinical trial
  - To ensure the trial is conducted according to *a priori* plan, including adaptation
- Structure
  - Learn phase: usually includes internal personnel
  - Confirm phase: generally includes only independent, external members

Data and Safety Monitoring Boards

- What's different in an adaptive trial?
  - Requires expertise to assess whether the planned adaptations continue to be safe and appropriate
  - May increase need to include sponsor personnel
- What's unchanged in an adaptive trial?
  - The DSMB ensures completion of the trial *as planned, including the adaptation*
  - It is the trial that's adaptive, not the DSMB

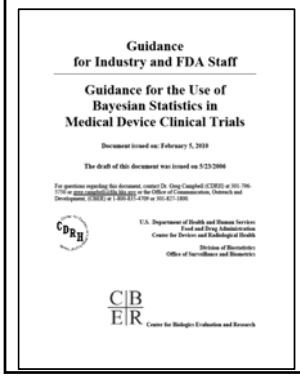
IRB Review

- IRBs review/approve the full protocol, including the planned adaptations
- No new review when adaptations made
  - IRBs may request to be informed (e.g., new sample size, dropping of a surgical arm)
- Amendments are different
  - Not preplanned
- Irony
  - Little changes (e.g., amendments) may require IRB review
  - Big changes (adaptations) are defined by design and only reviewed/approved once

Acceptability to Key Stakeholders

- FDA
  - FDA Critical Path Initiative
  - 2010 Guidance for the Use of Bayesian Statistics in Medical Device Trials
  - 2010 Draft Guidance for Adaptive Design Clinical Trials for Drugs and Biologics
  - Joint Regulatory Science initiative with NIH
  - Multiple adaptive trials accepted in development plans
- PhRMA
  - Highly active "working group" on adaptive trials → DIA
  - 2006 PhRMA/FDA Conference on Adaptive trials
  - Many adaptive trials designed or initiated in industry
- Peer reviewers may be unfamiliar with adaptive design principles

FDA Guidance Documents



Guidance
for Industry and FDA Staff

Guidance for the Use of
Bayesian Statistics in
Medical Device Clinical Trials

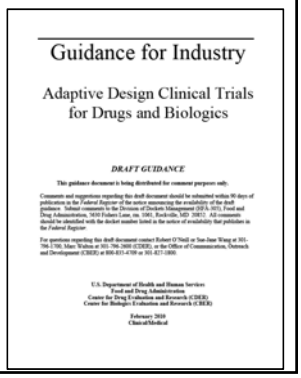
Document issued on: February 5, 2010

The draft of this document was issued on 5/23/2006

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Division of Biostatistics
Office of Surveillance and Biometrics

C|B
E|R
Center for Biologics Evaluation and Research



Guidance for Industry

Adaptive Design Clinical Trials
for Drugs and Biologics

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

February 2010
Clinical/Medical

The ADAPT-IT Project

- Supported by an NIH U01 grant with funds from both NIH and FDA
- Redesigning four clinical trials for treatments of neurological emergencies
  - control of blood sugar in stroke
  - hypothermia for spinal cord injury with paralysis
  - treatment of prolonged seizures
  - hypothermia after cardiac arrest
- Work closely with project teams and statisticians to create more efficient, ethical version of proposed trials

Online Tools and Resources

- MD Anderson
  - http://biostatistics.mdanderson.org/SoftwareDownload/
  - Lots of good utilities, including “Adaptive Randomization” to help with response adaptive trials
  - Allows 10 arms; minimum number of patients before adapting randomization scheme; maximum number of patients or length of trial
  - Free
- Commercial resources

Conclusions

- Not all trials need (or should have) adaptive designs
- When used appropriately, adaptive designs may:
  - Improve efficiency and reduce cost
  - Maximize the information obtained
  - Minimize risk to subjects and sponsor
- An adaptive design will not save a poorly planned trial or make a treatment effective