Society for Clinical Trials 31st Annual Meeting

Workshop P7
Adaptive Clinical Trials

Sunday, May 16, 2010
1:00 PM - 5:00 PM
Harborview Ballroom E
WORKSHOP 7 – Adaptive Clinical Trials

1. Overall, did the subject context of this workshop meet your expectations and needs?  
   Yes ( )  No ( )  
   If yes, in what way? If no, why not?  
   ____________________________________________________________  
   __________________________________________________________________________

2. Was the content of this workshop of value to you personally or on the Job?  
   Yes ( )  No ( )

3. Was the content of the workshop:  
   New ( )  New/Review ( )  Review ( )

4. The level and complexity of this workshop was:  
   Too elementary ( )  Correct ( )  Too advanced ( )

5. Rate the extent to which this workshop:  
   a. Presented content clearly  
      1  2  3  4  5
   b. Allowed sufficient time for discussion and audience participation  
      1  2  3  4  5
   c. Provided useful information  
      1  2  3  4  5
   d. Utilized appropriate teaching methods, i.e., audiovisual, handouts, lectures  
      1  2  3  4  5

6. Please rate each workshop faculty member:

<table>
<thead>
<tr>
<th>Name</th>
<th>Knowledge of Subject</th>
<th>Organization/Delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jason Connor</td>
<td>1 2 3 4 5</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>Roger J. Lewis</td>
<td>1 2 3 4 5</td>
<td>1 2 3 4 5</td>
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<tr>
<td>Jose Pinheiro</td>
<td>1 2 3 4 5</td>
<td>1 2 3 4 5</td>
</tr>
</tbody>
</table>
1. Are you currently working in a clinical trial? (Yes) (No)

2. What is your job title? __________________________________________________________

3. Do you have any suggested topics for workshops at future meetings? If so, please list below:
   ____________________________________________________________________________
   ____________________________________________________________________________

4. What aspect of the workshop did you like best?
   ____________________________________________________________________________
   ____________________________________________________________________________

5. What aspect of the workshop would you change if this workshop were offered again?
   ____________________________________________________________________________
   ____________________________________________________________________________

6. Additional Comments: _______________________________________________________________________________
Short Course:
Adaptive Clinical Trials

Presented at the 2010 Annual Meeting
of the Society for Clinical Trials
Baltimore, Maryland

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

Financial Disclosures

• Berry Consultants, LLC
• Kowa Research
• Octapharma USA
• AspenBio Pharma

Outline

• The "philosophy" of adaptive clinical trials
  – Planned change is good!
• Categories of adaptive trial designs
• 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

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

Begin Data Collection with Initial Allocation and Sampling Rules

- Analyze Available Data
- Continue Data Collection
- Stopping Rule Met?
- Revise Allocation and Sampling Rules per Adaptive Algorithm
- Stop Trial or Begin Next Phase in Seamless Design

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**

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Dose A</th>
<th>Dose B</th>
<th>Dose C</th>
</tr>
</thead>
<tbody>
<tr>
<td>N₁</td>
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</tr>
<tr>
<td>N₂</td>
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</table>

- **Rule**: Drop a dose if rate of AE1, AE2, or AE3 appears to be above the tolerable limit at either N₁ or N₂ based on lower limit of model-based 80% CI:
- **Limits**:
  - Pr(AE1) < 0.2
  - Pr(AE2) < 0.2
  - Pr(AE3) < 0.4

**Example**

<table>
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<tr>
<td>N₂</td>
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- No dose meets criteria for early termination so all will be continued until N₂.
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 \( \leq 2 \) 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
  - Sampling rule
  - Stopping rule
  - Decision rule

- 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
  - Response adaptive
    - Primary endpoint
    - Biomarker
    - Safety outcomes

The Adaptive Process

1. Begin Data Collection with Initial Allocation and Sampling Rules
2. Analyze Available Data
3. Continue Data Collection
4. Stopping Rule Met?
5. Revise Allocation and Sampling Rules per Adaptive Algorithm
6. Stop Trial or Begin Next Phase in Seamless Design
Components of an Adaptive Trial

Management

Adaptive Machinery

Logistics

Clinical

Drug Supply
Randomization System
CRO/Data Management

Site 1
Site 2
... Site n
Components of an Adaptive Trial

Management
- Sponsor
- Steering Committee
- Independent DSMB

Adaptive Machinery
- Adaptive Algorithm
- Data Analysis

Logistics
- Drug Supply
- Randomization System
- CRO/Data Management

Clinical
- Site 1
- Site 2
- Site n

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
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
Adaptive Dose-Ranging Designs and Methods

José Pinheiro
Johnson & Johnson PRD

Society for Clinical Trials Meeting
Adaptive Clinical Trials Workshop
Baltimore, MD - May 16, 2010

Outline

• Motivation and background
• Examples of Adaptive dose-ranging approaches
• Simulations for design and evaluation
• PhRMA Adaptive Dose-Ranging Studies WG
• Conclusions and recommendations

Motivation

• Poor understanding of dose response (DR) for both efficacy and safety is a pervasive problem in clinical drug development

• Indicated by both FDA and Industry as one of root causes of late phase attrition and post-marketing problems with approved drugs

• Current dose finding designs and methods: focus on dose selection out of fixed, generally small number of doses, via pairwise hypothesis testing ⇒ inefficient use of information
What is the problem?

- True DR model unknown
- Current practice:
  - Few doses
  - Pairwise comparisons
  - "dose vs. placebo"
  - Sample size based on power to detect DR

Large uncertainty about the DR curve and the final dose estimate

More efficient way: Adaptive Dose-Ranging

- Initially include few patients on many doses to "learn" interesting regions
- Then allocate more patients to the dose-range of interest

Adaptive Designs: what are they?

PhRMA WG 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 Dose-Ranging Designs

- **Dose allocation dynamically changed**, based on accumulating information on dose response
- Adaptation rule defined by **objective function**: e.g., minimize variance of target dose estimate, D-optimal design, etc
- Typically start with **larger number of doses**, focusing on fewer on relevant range
- Number of adaptations: **trade-off between flexibility and adapting on noise** (also logistics)
- Simulations are **key** to designing adaptive trial: evaluation of operational characteristics

### Adaptive Dose-Ranging Designs (cont.)

- Information needs to accumulate at pace that allows **meaningful adaptations**: trade-off between recruitment speed and effectiveness of adaptive algorithm
- Biomarkers and early readouts often used to drive adaptation, but not final dose selection
- Typically **model-based**, with Bayesian and frequentist implementations
- Additional adaptive rules often used in conjunction: **information driven** stopping rules (e.g., futility); sample size reassessment

### FDA draft guidance on AD

- Recently released (March 01), currently in comments period (deadline June 01)
- Overall **supportive** of AD, but particularly so in exploratory trials, such as dose-ranging
- Key regulatory concerns (mostly focused at trials with confirmatory component): type I error rate inflation and operational bias
- Key recommendations: keep it **simple** (few adaptations), **plan** thoroughly and in advance, increased interactions with FDA, and “squeaky clean” execution (firewalls, documentation, etc)
Examples of Adaptive DR Approaches

- Continuous Reassessment Method: CRM
- General Adaptive Dose Allocation: GADA
- D-optimal allocation, frequentist and Bayesian
- Adaptive MCP-Mod
- Interesting-Region of DR: IntR

All model-based, different objective functions for adaptation, varying degrees of complexity

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CRM

- Bayesian method originally proposed for Phase I cancer trials of cytotoxic agents with the goal of estimating maximum tolerated dose (MTD)
- For pre-defined set of doses and binary response, estimates MTD = dose that yields a particular target % of responses (e.g., TD20)
- Assumes a particular model (such as logistic), with Bayesian updating of parameters
- Doses are assigned to new cohorts of patients

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GADA

- Based on normal dynamic linear model (NDLM), a Bayesian non-parametric approach (flexible)
- Dose allocation aims to minimize variance of target dose estimate (e.g. ED95) – other obj. functions based on posterior dist. also possible
- Original formulation (used in ASTIN trial) updated model after each patient – less resource intensive version available (batches of patients)
- Used in combination with information-driven Bayesian stopping rules (futility, etc)
GADA algorithm (original version)

Simulations for trial design and evaluation

- Evaluation of operational characteristics (OCs) is critical step in design – comparison of methods
- OCs include power to detect signal, precision of estimates, expected duration, etc. In particular, determine sample size and number of arms
- Complexity of adaptive DR designs and other innovative dose finding methods typically no closed form expressions for OCs metrics
- Simulation-based evaluations are needed
- AD guidance: simulations key for AD trial design

Key goals of dose finding trials

- Determine evidence of DR signal, i.e., if average response changes with dose level – proof-of-concept (PoC)
- Select target dose(s) for confirmatory phase, e.g., MED, ED90
- Estimate DR profile – usually for efficacy, but safety of increasing interest
- These goals determine the design of the study and the OCs that need to be evaluated
**Trial simulation factors**

- Type: parallel groups, cross-over, titration, etc
- Available doses, inclusion of active control(s)
- Dose allocation scheme (fixed vs. adaptive)
- If adaptive, frequency and timing of adaptations (and algorithm for recalculating allocation ratios)
- Dose response profile(s):
  - more than one should be used to assess sensitivity
  - flat dose response should be included to assess Type I error rate and impact on dose selection

**Trial simulation factors (cont.)**

- Response: type (e.g., continuous, binary, count, ordinal); distribution (e.g., normal, Poisson)
- Possible covariates and their role in DR model
- Longitudinal measurements (when, how many)
- Var/cov parameters (e.g., within- and between patient variances, between-site variances)
- Sample size (e.g., expected, maximum)
- Drop-out and missing data models
- Accrual process (e.g., rates, uniformity over time)
- Stopping rules, if any (e.g., futility, efficacy)

**Trial simulation factors (cont.)**

- Number of simulations (OCs desired precision)
- Statistical analysis methods:
  - testing for DR signal
  - selecting target dose(s) – (target clinical effect?)
  - estimating DR profile
- Sensitivity analysis: impact of changes in assumed parameters/models/design on OCs (recommended)
- Choice of software: general purpose (e.g., Trial Simulator) vs. customized (e.g., R or S-PLUS)
PhRMA ADRS working group

• One of 10 WGs formed by PhRMA to address key drivers of poor performance in pharma industry

• Goals:
  – Investigate and develop designs and methods for efficiently learning about efficacy and safety DR profiles \( \Rightarrow \) benefit-risk profile
  – Evaluate OCs of diff. designs and methods (adaptive and fixed) to make recommendations on their use
  – Increase awareness about ADRS, promoting their use, when advantageous

• How: comprehensive simulation study comparing ADRS to other DF methods, quantifying potential gains

ADRS WG White Paper

Simulation study: design and assumptions

• Proof-of-concept + dose-finding trial, motivated by neuropathic pain indication (conclusions and recommendations can be generalized)

• Key questions: Whether there is evidence of dose response and, if so, which dose level to bring to confirmatory phase and how well dose response (DR) curve is estimated.

• Primary endpoint: Change from baseline in VAS at Week 6 (continuous, normally distributed)

• Dose design scenarios (parallel arms):
  – 5 equally spaced dose levels: 0, 2, 4, 6, 8
  – 7 unequally spaced dose levels: 0, 2, 3, 4, 5, 6, 8
  – 9 equally spaced dose levels: 0, 1, ..., 8

• Significance level: one sided FWER \( \alpha = 0.05 \)

• Sample sizes: 150 and 250 patients (total)
Dose response profiles

Methods considered

- ANOVA based on pairwise comparisons and multiplicity adjustment (Dunnett)
- MCP-Mod combo of multiple comparisons and modeling (Bretz, Pinheiro, and Branson, 2005)
- MTT: Multiple Trend Tests
- Bayesian Model Averaging: BMA
- Nonparametric local regression fitting: LOCFIT
- GADA
- D-opt: adaptive dose allocation based on D-optimality criterion

Target dose intervals

Target clinical effect: $\Delta = -1.3$ units (reduction in VAS)

<table>
<thead>
<tr>
<th>Target dose interval – doses that produce effect within $\pm 10%$ of target effect $\Delta$</th>
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<tbody>
<tr>
<td>Model</td>
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<tr>
<td>---</td>
</tr>
<tr>
<td>Linear</td>
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<tr>
<td>Logistic</td>
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<tr>
<td>Umbrella</td>
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<tr>
<td>Emax</td>
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<tr>
<td>Sig-Emax</td>
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</table>
SELECTED SIMULATION RESULTS


Power to identify DR

Dose selection under flat DR
Doses selected: umbrella, N = 150

PhRMA WG: Key conclusions

- Detecting DR is much easier than estimating it
- Sample sizes for DF studies are typically not large enough for accurate dose selection and estimation of DR
- Adaptive dose ranging methods and other innovative DF methods lead to substantial gains over traditional pairwise testing approaches (especially for estimating DR and selecting dose)
- No design/method uniformly best: relative performance depends on scenario, assumptions
- Approaches are multifaceted: e.g., adaptive, model-based, Bayesian, optimal design, etc

ADRS WG Recommendations

- Adaptive, model-based dose ranging methods should be routinely considered in Phase II
- Dose assignment algorithm should be prospectively and clearly specified in protocol
- Sample size calculations for DF studies should take into account precision of estimated dose
- When resulting N is not feasible, should consider selecting more than one dose for Phase III – preferably coupled with adaptive design
- PoC and dose selection should, when feasible, be combined in one seamless trial
ADRS WG Recommendations (cont.)

• Early stopping rules, for efficacy and safety, should be implemented, when feasible, to allow greater efficiency gains in adaptive design

• Potential gains associated with adaptive approaches should always be contrasted to additional complexity and costs related to their implementation – not a panacea

• Simulations should always be used in trial design

Acknowledgements

• Brenda Gaydos
• Chris Coffey
• Frank Bretz
• Björn Bornkamp
• Members of ADRS WG

References


Bayesian Adaptive Designs for Clinical Trials

Jason Connor
Presented at
Adaptive Clinical Trials Workshop
May 16, 2010

FDA Critical Path Initiative

From FDA website:
Many of the tools used today to predict and evaluate product safety and efficacy are badly outdated from a scientific perspective. We have not made a concerted effort to apply new scientific knowledge – in areas such as gene expression, analytic methods, and bioinformatics – to medical product development. There exists tremendous opportunities to create more effective tests and tools, if we focus on the hard work necessary to turn these innovations into reliable applied sciences.

http://www.fda.gov/scienceresearch/specialtopics/criticalpathinitiative/ucm077015.htm

What are Adaptive Trials?
Trials that change based on prospective rules & the accruing information

- Adaptive sample sizes based on predictive probabilities
  - Stop early for success
  - Terminate early for futility
- Adaptive randomization
  - For statistical efficiency
  - For improved patient treatment
  - Drop/Re-enter arms or dose groups
- Adaptive accrual rate
- Combination therapies
- Adapt to responding sub-populations
- Adaptive borrowing of information
- Seamlessly combine phases of development
Typical Prospective Adaptive Design

- Accrue & Randomize
- Initial Subjects
- Current Data State
- Statistical Modeling
- Accrue & Randomize More
- Adaptive Decisions & Actions
- Stop Accrual, Wait, Do Final Analysis
- Stop For Failure

The information in the data is critical
Interim values can be very informative
Guide adaptive features, not final conclusions

Answering the Right Question

- What will we know & when will we know it?
  - Consider accrual rate & timing of endpoints
  - Consider what adaptations we may want to make
  - Often can use historical/subjective priors in longitudinal model
  - but not final analysis
- What do we want to know?
  - Not p-value with current data
  - Probability of trial success if we stop enrolling now
  - Probability of trial success if we enroll to maximum
  - Probability of trial success if we drop a subgroup
- What will we want to know when this trial is over?
  - \( \Pr(\text{Efficacious}), \Pr(\text{Safe}) \)
  - In Phase 2 the probability we win a Phase III trial
  - Which dose is best (safest & most efficacious)
  - Which dose is most profitable

Time is Right for Adaptive Designs

- Janet Woodcock, FDA’s CDER Director, 2006
  - Improved utilization of adaptive and Bayesian methods could help resolve low success rate of and expense of phase 3 clinical trials
- Margaret Hamburg, FDA Commissioner 2010
  - “The final guidance on the use of Bayesian statistics is consistent with the FDA’s commitment to streamline clinical trials, when possible, in order to get safe and effective products to market faster.”
- CDRH produced guidelines for Bayesian statistics Feb 5, 2010
  - “Agency says Bayesian statistical methods could trim costs, boost efficiency” from press release
  - “They beauty is you do not end up doing a trial that is too big or too small; you end up doing a trial that is just right.” Greg Campbell
- CDER/CBER produced draft guidance for adaptive designs Feb 2010
Some Current Areas of Application

- Alzheimer's Disease
- Aneurysm
- Atrial Fibrillation
- Crohn's Disease
- Diabetes
- Emphysema
- Heart Valves
- HIV
- Lhido
- Lymphoma
- Lung Cancer
- Lupus
- Migraines
- Obesity
- Pre-term labor
- Spinal Cord Injury
- Spinal Implants
- Stroke
- Uterine Cancer
- Vaccines

Adaptive Designs & Collaborators

- Requires buy-in and educating IRB, DSMB, decision-makers, study teams, investigators, and subjects
- Requires more time, resources, and upfront planning, especially at the protocol-design stage
- Show sponsor many many example trials
  - Also great for debugging
- Complex study designs typically require more statistical assumptions, rigorous calculations, and extensive simulations (operating characteristics)
- But also more robust to deviations from our assumptions
- Operationally challenging
  - Work with CROs as early as possible, fit statistical parts within infrastructure
- Make sure sponsors understands what adaptive designs are not

Simulation

- Show a bunch of example trials
  - Don’t want surprises during the trial!
- Operating characteristics for a range of scenarios
  - Different efficacy profiles
  - Different accrual rates
  - Different decision rules
- Usually have to control Type I error rate by trial & error
  - Set critical value, run 10,000 sims, check Type I error
  - Adjust to get Type I error in worst case scenario at 2.5% or 5%
Why be adaptive?

- Doctor comes to you.
- Historical success rate = 50%
- Claims his therapy has 70% success
- “How many patients do I need to be statistically significant?”
If observed = 70% only need N = 30 not N=65!

Why be adaptive?

- Doctor comes to you.
- Claims his treatment increases IQ by 5 points
- SD = 10
- “How many patients do I need to have 90% power to demonstrate superiority?”

n = 166, σ = 10
Example in Neurology

- Goal:
  - Demonstrate efficacy & safety of neural implant
  - Pivotal device trial for FDA CDRH
  - Trial is underway enrolling patients
  - 1-armed trial vs. objective performance criteria
  - Sample size is 50 to 100 patients
  - First analysis with 50 patients
  - Interim analyses every 1 month
Trial Setup

• Primary Efficacy Outcome
  – 6-month success, \( p = \) success rate

• Primary Safety Outcome
  – No neurological safety event within 30-days of procedure, \( q = \) AE rate

• Compare to Objective Performance Criteria
  – Show \( p > 0.50 \) to demonstrate efficacy
  – Show \( q < 0.20 \) to demonstrate safety

Summary of Trial

• Efficacy
  – Observe \( x \) successes in \( n \) patients
  – Show \( \Pr(p > 0.50 \mid n, x) > 0.975 \)

• Safety
  – Observe \( y \) adverse events in \( n \) patients
  – Show \( \Pr(q < 0.20 \mid n, y) > 0.95 \)

• Priors: Likelihoods Posteriors:
  \( p \sim \text{Beta}(1,1) \)
  \( x \sim \text{Bin}(n, p) \)
  \( p \mid n, x \sim \text{Beta}(1+x, 1+n-x) \)

  \( q \sim \text{Beta}(1,1) \)
  \( y \sim \text{Bin}(n, q) \)
  \( q \mid n, y \sim \text{Beta}(1+y, 1+n-y) \)

Adaptive Sample Size

• Interim looks after 50 patients enrolled and 20 patients with 6-month outcomes
• Then re-analyze every month
• Calculate
  \( P_{n,x} = \) predictive probability of trial success with current sample size
  - If \( P_{n,x} \) high then Stop for Probable Success
  \( P_{n,100} = \) predictive probability of trial success if we enroll to maximum sample size
  - If \( P_{n,100} \) low then Stop for Futility
Adaptive Stopping Rules

• Stop enrolling for predicted success if
  \(- P_{n,n} > S_n \)
  \(- \) Wait 6-months for complete data \( \) do 1 final analysis

• Stop for futility if
  \(- P_{n,100} < F_n \)

<table>
<thead>
<tr>
<th>Sample Size</th>
<th>( S_n )</th>
<th>( F_n )</th>
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<tbody>
<tr>
<td>( n &lt; 60 )</td>
<td>0.99</td>
<td>0.05</td>
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<tr>
<td>( 60 \leq n &lt; 75 )</td>
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<td>0.05</td>
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<tr>
<td>( 75 \leq n &lt; 100 )</td>
<td>0.90</td>
<td>0.05</td>
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Predictive Probs using Partial Data

• At any interim analysis observe patients with Full data, Partial data, & No data

• First interim analysis with 50 patients
  \(- \) Accrued 5 patients per month

<table>
<thead>
<tr>
<th>Patients</th>
<th>50</th>
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<tr>
<td>Enrolled</td>
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<table>
<thead>
<tr>
<th>Follow-up</th>
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</tbody>
</table>
Interim Analysis: Safety

- \( n_S = 45 \) subjects provide full data for safety
- Observe \( y \) adverse events
- Calculate predictive prob. show safety with current \( n \)
  \[ q \sim \text{Beta}(1+y,1+y+n_{ij}) \]
- \( y^* \sim \text{Bin}(5, q) \sim \text{Beta-Binomial}(5, 1+y, 1+y+n_{ij}) \)
- \( y_T = y + y^* \) represents "complete" safety events
- Probability distribution for complete data set
- Calculate \( \Pr(q < 0.20 \mid 50, y_T) \) for \( y_T \in \{y, \ldots, y+5\} \)
- Pred probability of demonstrating safety with \( n \) patients
  \[ \sum_{k=0}^{\infty} \left[ \Pr(y_T = k) \times I(\Pr(q < 0.20 \mid n = 50, y_T = k) > 0.95) \right] \]

Interim Analysis: Efficacy

- At 50 patient analysis
  - 20 patients with 6-month data (complete), \( x \) successes
  - 15 patients with 3-month data
  - May be success or not at 3-month visit
  - 15 patients with < 3-month data
- Calculate probability distribution for complete data
  - \( x_T = x + x^*_o + x^*_s + x^*_f \)
  - \( x \) observed successes out of \( n \)
  - \( x^*_o \) predicted successes in patients with no follow-up
  - \( x^*_s \) predicted successes in patients who are successes at 3-months
  - \( x^*_f \) predicted successes in patients who are failures at 3-months

Use Historical Data to form Priors

- Want to predict 6-month success for
  - Patients without 3-month follow-up: 83%
  - Patients successes at 3-months: 90%
  - Patients failures at 3-months: 50%
- Use priors each equal to 6-patients worth of info
- Priors only used to determine sample size
  - Not used in final analysis so okay to be informative
  - Incentive to be 'honest' otherwise could stop too early

<table>
<thead>
<tr>
<th>Group</th>
<th>Prior</th>
<th>Prior Mean</th>
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</thead>
<tbody>
<tr>
<td>No 3-month follow-up</td>
<td>( \alpha_o \sim \text{Beta}(3.0, 1.0) )</td>
<td>0.83</td>
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<tr>
<td>Success at 3-month</td>
<td>( \alpha_s \sim \text{Beta}(5.4, 0.6) )</td>
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<tr>
<td>Failure at 3-month</td>
<td>( \alpha_f \sim \text{Beta}(3.0, 3.0) )</td>
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</tbody>
</table>
Predict Efficacy Data

- At 50 patient analysis, \( c_{++} = 20 \) completers

<table>
<thead>
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<th>Group</th>
<th>Posterior</th>
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</thead>
<tbody>
<tr>
<td>No 3-month follow-up</td>
<td>( s^* \mid \text{Interim Data ~ Beta-Bin}(5.0+c_{++}, 1.0+c_{++}) )</td>
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<tr>
<td>Success at 3-month follow-up</td>
<td>( s^* \mid \text{Interim Data ~ Beta-Bin}(5.4+c_{++}, 0.6+c_{++}) )</td>
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<tr>
<td>Failure at 3-month follow-up</td>
<td>( s^* \mid \text{Interim Data ~ Beta-Bin}(3.0+c_{++}, 3.0+c_{++}) )</td>
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</table>

Predict Efficacy Data

- Calculate \( \Pr(p > 0.50 \mid 50, n) \) for \( n \in \{20, \ldots, 50\} \)
- Pred probability of demonstrating efficacy with \( n \) patients

\[
P_{x,n}^E = \sum_{j=0}^{30} \left[ \Pr(x_f = x + j) \times \mathds{1}(\Pr(p > 0.50 \mid 50, x_f = x + j) > 0.975) \right]
\]

- Repeat predicting with 100 patient data set, \( P_{x,100}^E \)

\[
P_{x,100}^E = \sum_{j=0}^{80} \left[ \Pr(x_f = x + j) \times \mathds{1}(\Pr(p > 0.50 \mid 100, x_f = x + j) > 0.975) \right]
\]

Calculating \( P_{n,n} \)

To win @ 50pts:
- Efficacy \( \geq 32 \)
- Safety \( \leq 3 \)

Observe:
- Efficacy \( x = 18 \) of 20
  - 30 to be predicted
- Safety \( y = 2 \) of 45
  - 3 to be predicted
Observe:

\[ x = 18 \text{ of } 20 \]

30 to be predicted

\[ x^T \in \{18,\ldots,48\} \]

\[ y = 2 \text{ of } 45 \]

5 to be predicted

\[ y^T \in \{2,\ldots,7\} \]

---

### Operating Characteristics

<table>
<thead>
<tr>
<th>(\rho)</th>
<th>(\eta)</th>
<th>True Eff</th>
<th>True Safe</th>
<th>Power = Prob We Show</th>
<th>Stopping Decision</th>
<th>Sample Size</th>
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Bayesian Adaptive Designs
- Fundamental change in the way we conduct medical research
  - Look at the data early & often
  - Make prospectively defined adaptations & decisions
  - Base decisions on predictive probabilities
- Better treatment of patients in & out of trials
- More rapid progress
- Lower development costs
- Accepted by regulators
- More fun for statisticians