

Adaptive Designs :- An overview

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Adaptive Designs

“Clinical trials can be designed with *adaptive* features (i.e., changes in design or analyses guided by examination of the accumulated data at an interim point in the trial) “that may make the studies more **efficient** (e.g., shorter duration, fewer patients), “more **likely to demonstrate an effect of the drug** if one exists, or more **informative** (e.g., by providing broader dose-response information).”

FDA Guidance for Industry Adaptive Design Clinical Trials for Drugs and Biologics, 2010

Introduction

It has been almost 6 years since February 2010 and the release of the FDA Draft Guidance for Industry: Adaptive Design Clinical Trials for Drug and Biologics, Utilization of adaptive designs within industry seems to have plateaued.

Objectives of this presentation is limited to below points.

- When is it advantageous to utilize adaptive trial designs?
- What are the best practices for implementation of adaptive trial designs?

Approach in Adaptive Designs

The planning should be done for adaptive designs on three different phases, Initial, Interim and Final. Some of examples are

- Adaptive randomization
- Bayesian analysis
 - › multiple subject randomization lists
 - › interim looks at data
 - › data integration with EDC
- Decision rules
 - › Allocation Rule: how subjects will be allocated to available treatment arms
 - › Sampling Rule: how many subjects will be sampled at the next stage
 - › Stopping Rule: when the clinical study will stop (for efficacy, safety, futility)
 - › Decision Rules: final and interim decisions pertaining to design change not covered by the previous three rules

Approach in Adaptive Designs

- Dose Escalation
- Sample Size Recalculation/Determination

Benefits to Adaptation:

- Improve understanding and identify successful trails earlier
- Lower development costs
- Ability to drop unnecessary treatment arms or determine effective doses sooner
- Utilized to cope with difficult “experimental” situations
- Expedite the research process with more flexibility
- **Forethought:**
 - Adaptations described and justified in protocol
 - Higher level of planning and teamwork
 - Too many adaptations make a trial exploratory

Requirements for implementation of Adaptive Trial Design:

- Ability to quickly, safely and effectively respond to trial decisions
- Change sample size
- Implement stopping rules such as deactivating clinical sites
- Recalculate drug supply quickly and accurately
- Implement complex randomization schemes
- Ability to access clean data quickly
- Ability to access real time reporting to monitor study progress
- Ability to develop realistic detailed simulation data
- Plan for security of unblinded information

Utilizing Technology

Utilizing IVRS/IWRS and EDC solutions to meet Adaptive Design needs

- Implementation of complex randomization schemes
- Switch and randomization schemes seamlessly
- Open and close treatment arms within seconds
- Add or remove dose levels within seconds
- Global drug supply management
- System programming to manage multiple drug supply factors
- Labeling groups
- Expiry dates
- Supply chain levels
- Supply demand and projections

Utilizing Technology

EDC can address the following needs:

- › Access clean study data as quickly as possible in order to make decisions
- › Efficient data management
- › Ability to clean quickly
- › Real time reports/alerts to notify key personnel of study progress

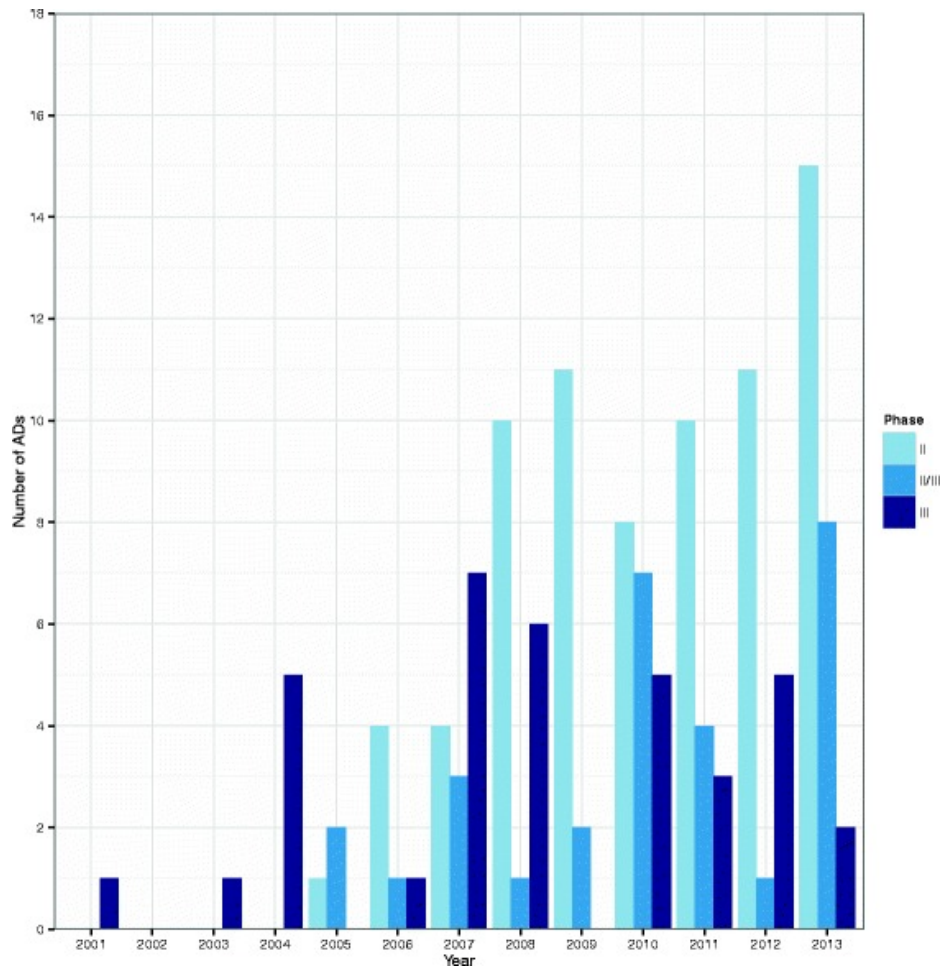
Design for Successful Adaptive Supplies Management

- Supplies should be packaged in the smallest possible components to allow maximum benefit of adaptive supplies management
 - › One kit per visit is recommended
 - › If more than one type of drug is provided per patient at a visit, package each separately for maximum flexibility
- Use booklet labels where possible
 - › Titration (fixed vs. flexible)
 - › Dosing (calculation)
- Many advantages to supply forecasting
 - › Simulates clinical supply demand
 - › Program or protocol specific
 - › Project time phased demand at the patient level

Design for Successful Adaptive Supplies Management

- Simulates supply chain demand
 - › Forecasts material requirements
 - › Projects inventory and safety stock
- Optimizes supply strategies
 - › Correlates supply and demand
 - › Projects multiple scenarios
 - › Allows for real time adjustments with live data

Bar chart showing the number of ADs per year*

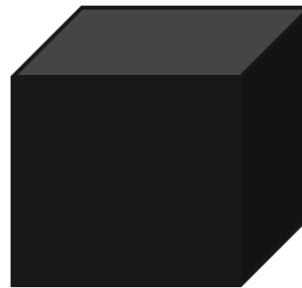


How it is different from usual

Prespecify before starting:

- Effect size
- Sample size
- Randomization ratios
- Primary and Secondary Endpoints
- Study eligibility criteria
- Treatment regimens
- Schedule of patient evaluations for data collection

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“Black Box”

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Possible causes for failure when trial is over:

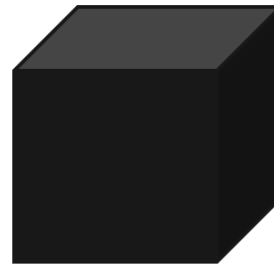
- Wrong effect size estimate
- Poor choice of primary endpoint
- Inadequate sample size
- Greater than anticipated variability
- Eligibility criteria too restrictive and enrollment low
- Doses chosen too high (toxicity) or too low (ineffective)

Adaptive Design

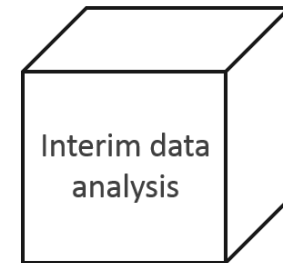
Prospectively specify before starting:

- One or more blinded or unblinded interim data analyses
- Specific potential interventions for anticipated issues with:
 - Sample size
 - Randomization ratios
 - Primary and Secondary Endpoints
 - Study eligibility criteria
 - Treatment regimens

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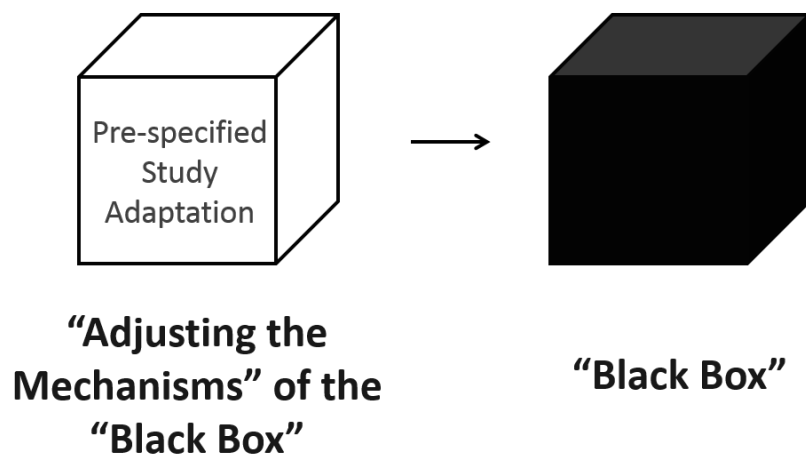
“Black Box”



**“Peeking” into the
“Black Box”**



Adaptive Design



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Reduced causes for failure when trial is over:

- Extended enrollment to overcome:
 - Inaccurate effect size estimate
 - Inadequate sample size
 - Greater than anticipated variability
- Adjusted eligibility criteria to more realistic population
- Elimination of toxic or ineffective dose arms
- Adjusted randomization to "winning" study arms

Key Points to Remember

- Why we need more flexibility
 - › Sample size not correct (response differs from expectations)
 - › Endpoint is not OK
 - › Does not differentiate between treatments or treatment effect
 - › Objectives change
 - › Superiority was an overly ambitious goal
 - › Wrong treatments or doses
 - › Suboptimal statistical methodology
- Maintaining integrity and validity
 - › Providing correct statistical inference
 - › Assuring consistency between study stages
 - › Minimizing bias
 - › Providing convincing results to a broad scientific community
 - › Preplanning as much as possible based on intended adaptations
 - › Maintaining confidentiality

Key Points to Remember

- Lower development costs
 - › Stopping unsuccessful trials earlier
 - › Identifying successful trials sooner
 - › Dropping unnecessary treatment arms
 - › Determining effective dose regimens faster

Challenges

Why are we still seeing relatively few adaptively designed trials?

- Actual gains are rather small
- Theory not widely understood
- Concerns regarding loss of credibility
- Regulatory acceptability
- Concerns about Operational Bias

Thank you!
Questions?

Reference

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