U.S. FOOD & DRUG ADMINISTRATION

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FDA/CDRH Webinar

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Adaptive Designs for Medical Device Clinical Studies

Final Guidance

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Agenda

- Guidance Background
- Adaptive Design definition, benefits and limitations
- When to Choose an Adaptive Design?
- Adaptive Design Considerations and Approaches
- Adaptive Design in Centers for Devices and Biologics
- Question & Answer

Adaptive Designs for Medical Device Clinical Studies

Guidance for Industry and Food and Drug Administration Staff

Document issued on July 27, 2016.

The draft of this document was issued on May 18, 2015.

U.S. Department of Health and Human Services
Food and Drug Administration

Center for Devices and Radiological Health

What are Adaptive Designs?

- Studies that include a prospectively planned opportunity(ies) to change the study design based on accumulating data during the course of the study without undermining study integrity and validity.
  - This potentially includes modifications after a trial is underway but before unmasking/unblinding
  - Does NOT include retrospective or *ad hoc* changes introduced after outcomes are known, nor attempts to salvage failed trials

Why Consider an Adaptive Design?

- Clinical study designs are based on expected outcomes, including event rates for treatment and control groups, accrual rates, dropout rates, variances, etc.
- If everything goes exactly according to plan, then a fixed trial design is optimal.
- But these original assumptions are really only guesses and are often far off.
- **Adaptive designs can address moderate levels of uncertainty in these assumptions.**

Adaptive Designs

- Can be frequentist or Bayesian
  - CDRH and CBER have experience with both types
- Adaptive designs are usually analyzed in stages, with potential adaptations pre-specified for each stage.
- For device submissions, the adaptation needs to be planned in great detail before any unblinded data are observed.

Examples of adaptations

- Sample size adjustment, including:
  - Group sequential designs
  - Sample size re-estimation
  - Adaptive recruitment (Bayesian)
- Adaptive randomization
- Changes to study eligibility criteria (patient inclusion/exclusion)
- Drop/add/change treatment arms
- Changes to Statistical Analysis Plan or Hypotheses
- Endpoint changes
- Study duration

Differences between a Fixed and Adaptive Trial

FACTOR	FIXED TRIAL	ADAPTIVE TRIAL
Number of patients	Fixed	Variable
Patient population	Fixed	Can be narrowed
Randomization	Constant probability	Can be adjusted
Primary hypothesis	Fixed	Can be changed
Decision rules	Simple	Complex

Adaptive Design Pros and Cons

PRO	CON
Efficiency (patients, duration, money)	Complexity
May be shorter duration	Unknown duration, possibly longer
More likely to succeed	Results may be harder to interpret
Fail quickly	Harder to conduct
Patient protection	Potential operational bias
Flexibility	Not as flexible

Should a trial be adaptive?

- Feasibility:
  - If there is time to adapt.
    - i.e. if all the patients are enrolled before any outcomes are known there is no time to make any changes.
  - If there are multiple important endpoints it may not be possible to simultaneously adapt for all of them.
  - If sample size is driven by safety concerns then adapting on effectiveness won't be feasible.

Should a trial be adaptive? Contd.

- Advantageous if:
  - There is some uncertainty in design parameters that can be addressed by adapting.
  - The operating characteristics of the adaptive design are favorable over a wide range of plausible scenarios.
    - Especially consider “anticipated regret” scenarios
  - There are clear advantages over the alternative fixed design.

Should a trial be adaptive? Contd.

- NOT advantageous if:
  - There are too many unknowns that affect which design is optimal
  - Design parameters are not known with sufficient precision to allow efficient adaptation
  - The gain over a fixed design is small

What phases?

- Adaptive designs can be used at any phase of development
  - Dose finding studies are often adaptive
  - Seamless phase II/III studies
  - Pivotal studies
- CDRH experience is almost entirely with pivotal studies. CBER has more experience with early phases.
- From regulatory perspective, most concern/interest is in pivotal studies

Regulatory concerns

- Type I error control
  - Operating characteristic of design
- Estimation of treatment effect
  - Appropriate estimates & confidence intervals
- Operational bias
  - Who knows what, when, and how it affects behavior that might bias the results of the study
- Power considerations
- Practical considerations
  - Trial infrastructure, conduct

CDRH experience

- 251 adaptive studies 2007-2013*
  - Mostly designs (IDEs)
  - Some (32) product submissions (PMA, 510(k))
- Overwhelming majority are sample size related adaptations
  - Frequentist (156/176 sample size related adaptations)
    - Group sequential, sample size re-estimation
  - Bayesian (67/75 sample size related)
    - Sample size re-estimation
    - Adaptive recruitment

*Yang et. al., 2016. "Adaptive Design Practice at the Center for Devices and Radiological Health (CDRH), January 2007 to May 2013" Therapeutic Innovation and Regulatory Science 1-8.

Blinded studies

- If blinding is scrupulously maintained:
  - Adaptations are more easily accomplished.
  - There are less questions about statistical or operational bias.
  - Changes based on aggregate results can often be incorporated.

Adaptive Sample Size

- Why plan to adapt the sample size?
  - Estimates of important parameters that are used to size a study are often (usually) different than what is observed in the study and results in either over- or under-powered studies.
- Sample size re-estimation can correct this problem to some degree, using estimates obtained at interim looks to revise the sample size for the study.

Frequentist Adaptive Sample Size

- Group sequential designs
- Sample size re-estimation (frequentist)
  - Conditional power
  - Conditional type I error
  - P-value combination
  - Etc.
- Internal pilots
  - Maintain blind, only estimate nuisance parameters

Bayesian Adaptive Sample Size

- Bayesian approaches:
  - Often employs frequent interim analyses
    - Decision rules based on predictive probability
  - Includes adaptive recruitment
    - Recruitment ends when predictive probability of success is sufficiently large
  - Includes group sequential designs

General Approach to Adaptive Sample Size

- Fix sample size for stage 1, calculate appropriate summary
  - test statistics/conditional power/predictive distribution/etc.
- Decision rule: stop (futility), stop (success), recruit more patients
  - Potentially re-estimate sample size based on outcome
  - Continue to next stage
  - Repeat as necessary (with pre-specified max # of looks)
- Compute overall test statistic using an appropriate method that controls type I error

Adaptive enrichment

- At interim analysis, evaluate results overall as well as within pre-specified subgroups
- Interim decision options:
  - Stop study (futility, success)
  - Continue with entire population
  - Continue, but restrict to some subset of pre-specified subgroup(s)
- Use appropriate design/analysis/decision rules (frequentist or Bayesian) that control type I error

Sample size vs. Enrichment

- Sample size adaptations can protect against poor estimates of important parameters (e.g. effect size) at design stage.
- Adaptive enrichment can protect against poor choices of appropriate patient population.
  - False positives in preliminary studies
  - Perhaps covariate influence on outcome is not clear

Simulations

- For complex designs, extensive simulations are needed to fully characterize operating characteristics of the design.
- Simulations can help inform operational plans – identify and plan for possibilities before they arise
- The details matter, should design the simulation like an experiment (need appropriate coverage of the parameter space)
- Basic programming mistakes do sometimes occur – importance of independent coding, etc.

Bias control

- Operational bias can occur if information regarding the progress of the trial leaks out.
- If participants (patients, investigators, analysts) change their behavior based on emerging results then the trial results will be biased.

Solution: maintain appropriate “firewalls” so that only those who need to know have access to randomization and outcome data.

Operational Challenges

- Adaptation/steering committee
  - Determines when to adapt trial
- Data Monitoring Committees (DMCs)
  - Primary role is protecting patients
  - Sometimes charged with determining adaptations
  - Require DMC Statistician with Adaptive Design knowledge
- Operational bias
  - A concern in all trials, but especially adaptive trials
  - Try to reduce ‘information leakage’ as far as possible

Operational Challenges Contd.

- Institutional Review Boards (IRBs)
  - Primarily concerned with safety
  - Need advance planning to minimize delays in IRB approval of adaptations
- Logistics
  - Need smooth data flow and checking for timely adaptation
  - Need common understanding of how trial will be conducted
  - Need supplies, etc. to accommodate changes to treatment

Interactions with CDRH/CBER

- Earlier is better
  - Use pre-submission process as outlined in guidance.
- At design stage, operating characteristics will be of concern to FDA
  - If using simulation, cover a wide range of possible scenarios.
- Monitoring plan will be important.
- Other techniques (blinding, firewalls, etc.) to reduce operational bias

CBER's Devices

- A few are therapeutic
- Products to process blood, cells and tissues
- Some trials are similar to trials for biologics
- Most adaptive and/or Bayesian submissions have been for biologic products
- Protocol assessments similar for Investigational Device Exemptions (IDEs) and Investigational New Drugs (INDs)

CBER's Survey of Adaptive Designs

- Survey* covers 2008-2013; seeing more now.
- Bayesian methods common in phase 1 and 2 (oncology)
- Proposals for Bayesian adaptive studies in phase 3
- Proposals for adaptive designs with type 1 error via simulation
- May take more than one round of discussion to finalize
- Clinical as well as statistical considerations are important

*Lin, M., S. Lee, B. Zhen, J. Scott, A. Horne, G. Solomon, E. Russek-Cohen (2016) CBER's Experience with Adaptive Design Clinical Trials. Therapeutic Innovation and Regulatory Science 50:195-203.

Diagnostics

- Prevalence of rare conditions will often drive sample size in diagnostic performance studies.
- Protocols for prospective studies can define a rule to add samples based on observed prevalence as defined by a reference method.
  - No alpha penalty.
- Banked specimens are sometimes allowed.
  - First contact review division.

Thank you

Questions?

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Slide Presentation, Transcript and Webinar Recording will be available at:

http://www.fda.gov/training/cdrhlearn

Under Heading: How to Market Your Device;
Sub-heading: Clinical Studies/IDE


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