Adaptive Designs for Clinical Trials of Drugs and Biologics: Draft Guidance for Industry

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Outline

- Background
- Adaptive design draft guidance
  - Introductory concepts
  - Key principles from a regulatory perspective
  - Adaptations based on non-comparative interim results
  - Adaptations based on comparative interim results
  - Special considerations and topics
  - Maintaining trial integrity
  - Regulatory considerations
  - Public comments and next steps

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PDUFA VI and/or 21st Century Cures Act Commitments

- Develop staff capacity
- Pilot program
- Public workshop (March 20, 2018)
- Draft guidance on complex adaptive trial designs and simulations/technical feedback
- MAPPs, SOPPs, and/or review templates

Complex Innovative Design (CID) Pilot Program

- Started in 2018, 5-year duration
- Joint CDER/CBER effort
- Sponsors gain additional interactions with FDA to discuss proposed design
- FDA gains ability to publicly discuss aspects of the trial design and share learnings
- FDA will select up to 2 submissions per quarter
- Information at: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm617212.htm

Adaptive Design Guidance (CDER/CBER)

- New draft published in September 2018
  - Replaced 2010 draft
  - Moves away from categorization as well-understood or less well-understood
  - Focuses on key principles in design, conduct, analysis, and reporting
  - Expanded discussion on technical aspects such as estimation, simulations, Bayesian methods
  - Added clarity on information FDA requests for review

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What is an Adaptive Design?

- A clinical trial design that allows for prospectively planned modifications to one or more aspects of the design based on accumulating data from subjects in the study
- It is not:
  - Unplanned changes based on comparative interim results (sponsor should meet with FDA!)
  - Protocol amendments based on information from sources external to study (often ok if confidentiality to comparative results maintained)

Motivation for Adaptation

- Advantages in statistical efficiency
  - e.g., a greater chance of detecting a drug effect at a given expected sample size
- Ethical advantages
  - e.g., stop trial if data not consistent with an effective drug (futility) or if persuasive evidence of important effect (efficacy)
- Advantages in understanding of drug effects
  - e.g., improved estimation of dose-response relationship in study with adaptive dose selection

Limitations of Adaptation

- Methodology challenges in ensuring control of chance of erroneous conclusion, reliability in estimation (e.g., bias, CI coverage)
- Operational challenges in maintaining confidentiality and trial integrity
- Potential challenges in interpretability due to changes in estimand of interest

When to Adapt?

- Trial design decisions depend on many factors, both scientific and non-scientific
- FDA should not require or forbid use of adaptive designs in general or specific settings
- Good practice for sponsors to explore operating characteristics for variety of design options, discuss considerations with FDA at regulatory meetings prior to phase 3

Important Distinctions

- Exploratory studies versus studies intended to provide substantial evidence of effectiveness
  - Focus today mostly on latter
- Accumulating study data that are *comparative* versus *non-comparative*
  - Often called *unblinded* versus *blinded*
  - Adaptations based on comparative results typically affect operating characteristics such as Type I error probability, require special statistical methods

Types of Adaptive Designs

- Adaptations based on non-comparative data
  - Adaptations based on baseline characteristics
  - Adaptations based on pooled outcome data
- Adaptations based on comparative data
  - Group sequential designs
  - Adaptations to the sample size
  - Adaptations to the patient population
  - Adaptations to treatment arm selection
  - Adaptations to patient allocation
  - Adaptations to endpoint selection

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Regulatory Principles for Adaptive Designs

(1) Chance of erroneous conclusions should be adequately controlled

(2) Estimation of treatment effects should be sufficiently reliable

(3) Details of design should be completely pre-specified

(4) Trial integrity should be appropriately maintained

Controlling the Chance of Erroneous Conclusions

- Limit probability of bad decisions, e.g., caused by incorrect conclusions of safety or effectiveness, incorrect conclusions of lack of safety or effectiveness, or misleading estimates contributing to evaluation of benefit-risk
- Effectiveness typically demonstrated through test of null hypothesis (e.g., at 1-sided 2.5% level)
  - Adaptive designs can inflate type I error probability
  - Should utilize testing method with error probability control supported by theory or comprehensive simulation

Ensuring Reliable Estimation

- Accurate and precise estimates important to ensure regulatory decisions based on reliable benefit-risk evaluation and appropriate labeling to enable evidence-based medicine
- Adaptations induce bias in estimates, incorrect confidence interval coverage
- Use methods for adjusting estimates where available, evaluate extent of bias and present/interpret with caution where not

Complete Pre-specification

- Prospective planning should include anticipated number and timing of interim analyses, type of adaptation, statistical methods to be used at interim and final analysis, anticipated algorithm governing adaptation decision
  - Facilitates use of appropriate inferential methods for many types of adaptations
  - Increases confidence that adaptations not based on accumulating knowledge in unplanned way
  - Motivates careful planning, reduces desire for sponsor access to comparative interim data, ensures that DMC (if involved in adaptive process) focuses on patient safety and trial integrity

Complete Pre-specification

- Prespecification of adaptation rule is recommended but it is understood that monitoring committee recommendations may occasionally deviate from anticipated algorithm based on totality of data
- If such flexibility desired, analysis plan should:
  - Acknowledge possibility of deviations
  - Outline factors that may lead to such deviations
  - Propose testing and estimation methods that do not rely on strict adherence to algorithm
  - Talk to FDA when completely unforeseen circumstances arise

Maintaining Trial Integrity

- Recommended in all trials that access to comparative interim results limited to individuals independent of personnel conducting or managing the trial
- Additional challenges in context of adaptive design
- Additional discussion later

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Adaptations Based on Pooled Outcome Data

- Sample size depends on significance level, power, targeted effect size, nuisance parameters
- Nuisance parameters: not of primary interest but affect statistical comparisons
  - Variance with continuous outcome
  - Event rate on control arm with binary outcome
- Often uncertainty in these factors at design stage
- Goal: use accumulating information about nuisance parameters (e.g., interim estimate of variance) to modify sample size to maintain desired power

Case Study

- Clinical trial to evaluate eliprodil for treatment of patients with severe head injury[2]
- Primary efficacy endpoint was 3-category outcome defining functional status at 6 months
- Uncertainty at design stage in proportions of placebo patients expected to experience 3 functional outcomes
- Interim analysis to update estimated proportions based on pooled, non-comparative data and potentially increase sample size ⇒ avoid inadequately powered study
- Adaptation led to sample size increase from 400 to 450

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Group Sequential Designs

- Allow stopping trial early for efficacy, lack of efficacy, or harm to better address ethical, economic issues
  - Trial participants not unnecessarily exposed to inferior treatments
  - Individuals outside trial provided more effective treatment options ASAP
  - Economic benefits by reduction in average sample size and/or calendar time of trial, accelerating adoption of new treatments

Case Study: PARADIGM-HF

- Clinical trial comparing LCZ696 (sacubitril/valsartan) to enalapril with respect to risk of CV death or hospitalization for heart failure in patients with chronic heart failure with reduced ejection fraction[8]
- 3 interim analyses when 1/3, 1/2, and 2/3 of total planned number of events occurred
- Pre-specified rules for stopping trial for efficacy
- Trial ultimately stopped at 3rd interim analysis with compelling evidence of superiority of LCZ696
  - More rapid determination than fixed sample design

Other Types of Adaptations Based on Comparative Interim Results

- Adaptations to the sample size
  - "Promising Zone"
- Adaptations to the patient population
  - Adaptive enrichment
- Adaptations to treatment arm selection
  - Adaptive dose selection or platform trials
- Adaptations to patient allocation
  - "Play the winner" or covariate-adaptive assignment
- Adaptations to endpoint selection
- Adaptations to multiple design features

Case Study

- "Seamless Phase IIb/III" trial to evaluate 9-valent HPV vaccine[23]
- 1,240 young women randomized to 1 of 3 dose formulations or active control (4-valent vaccine)
- Interim analysis to select 1 dose to carry forward
- 13,400 additional women randomized to selected HPV-9 dose or HPV-4
- Data from all subjects used in final analysis

Case Study: STAMPEDE

- Clinical trial compared androgen deprivation therapy (ADT) with several treatment regimens combining ADT with one or more approved therapies in prostate cancer[24]
- Multiple interim analyses to potentially drop treatment arms not performing well
- Use of common control group and sequential analyses to drop arms allowed efficient evaluation of several treatments

Case Study: PREVAIL II

- Clinical trial evaluated ZMapp plus standard of care versus standard of care alone for treatment of patients with Ebola virus disease[27-28]
- Interim analyses after every 2 patients completed (no potential action into 12 per group)
- Decision rules for concluding efficacy based on Bayesian posterior probability that ZMapp reduces 28-day mortality
- Also opportunity to add new experimental arms

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Special Considerations and Topics

- Simulations in Adaptive Design Planning
- Bayesian Adaptive Design
- Adaptations in Time-to-Event Settings
- Adaptions Based on a Potential Surrogate or Intermediate Endpoint
- Secondary Endpoints
- Safety Considerations
- Adaptive Design in Early-Phase Exploratory Trials
- Unplanned Design Changes
- Design Changes Based on External Information

Simulations: What to estimate

- Type I error probability
  - Other clinically relevant error probabilities
- Power
  - Possibly under various alternatives
- Expected sample size
- Estimation properties
- Bayesian alternatives

Simulations: Some Considerations

- Reducing and spanning the null space to estimate Type I error probability
  - Limit the null space based on clinical considerations
  - Do grid-based spans of the remaining space
  - Take advantage of monotonicity, regularity, or other mathematical arguments when available
- Sufficient number of iterations to provide precise estimates
- Comprehensive simulation report for review

Simulation Report

- Overall description of design
- Example trials
- Description and rationale of simulation scenarios chosen
- Simulation results (operating characteristic estimates and CIs)
- Simulation code
  - Readable, adequately commented, include random seeds used
- Summary / conclusions

Bayesian Adaptive Design

- Designs that use Bayesian statistical reasoning and/or calculations
  - Bayesian calculations can be used in either a Frequentist or Bayesian inferential framework
- Examples
  - Any use of posterior distribution to guide decisions
    - Group sequential design with stopping rules on Bayesian scale
  - Explicitly borrowing control arm information from earlier study or other external data with an informative prior
  - Explicitly borrowing both control and treatment arm information (or treatment effect information) from earlier study with an informative prior

Bayesian vs. Frequentist Inference

- Not all trials with Bayesian calculations use Bayesian inference
  - Frequentist inference characterized by hypothesis tests performed with known Type I error probability and power
  - Bayesian inference characterized by drawing conclusions based on posterior probabilities that a drug is effective
- Bayesian inference proposals require careful consideration of priors and of decision criteria

Safety Considerations

- Adaptations can be based on safety endpoints
- Adaptations on efficacy endpoints can have safety implications as well
- Stopping a trial too early can prevent accumulation of adequate safety database
    - E.g. many vaccines require 3,000 subjects exposed to support licensure
- In some cases, adaptations can affect trial subject safety
  - E.g. dose escalation
- Careful planning helps mitigate these risks

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Why Limit Access to Interim Results?

- Provides greater confidence that potential unplanned design modifications are not motivated by accumulating data
- Helps ensure quality trial conduct
  - Knowledge of interim results can affect:
    - Patient accrual
    - Adherence
    - Treatment assignment
    - Retention
    - Endpoint assessment

How to Limit Access

- An independent body should implement adaptive decision-making
  - An independent adaptation committee
  - DMC (primary focus still patient safety and trial integrity)
- Safeguards to ensure persons who prepare and report interim analysis results physically and logistically separated from personnel tasked with managing and conducting the trial
- Confidentiality agreements
- Logistical and physical firewalls to prevent access to critical data elements including treatment assignment
- Data access plan specifying
  - Who has access to confidential data
  - When that access occurs
  - What types of data and results are involved

Who Has Access

- Generally access should be avoided for patients, investigators, research staff, sponsor personnel
- The committee (Adaptation Committee or DMC) charged with making recommendations should have appropriate expertise
  - Including statistician(s) knowledgeable about the methodology, the monitoring plan, and the decision rules
- The committee's responsibility should be to make recommendations based on pre-existing adaptation plan, not to propose new adaptations based on review of data
- The committee should therefore be involved at the design stage in extensive discussion about possible scenarios and whether the adaptation plan provides sensible actions

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Interactions with FDA

- Purpose depends on development stage
  - Early phase review typically focuses on subject safety rather than validity of inference
  - Early phase design feedback may be available and can be the basis for requesting a Type C meeting
- For late-stage trials in particular, early and more extensive interaction may be appropriate
  - Mechanisms include Type C meetings, EOP2 meetings, CID Pilot program, sometimes pre-IND meetings

FDA Review of Adaptive Designs

- For late-stage trials FDA will evaluate whether the design and analysis of an adaptive design proposal satisfies key principles outlined today:
  - Chance of erroneous conclusions controlled
  - Reliable estimation of treatment effects
  - Trial integrity maintained
- Often good practice to have explored a variety of adaptive and non-adaptive design candidates

Documentation Prior to Conducting an Adaptive Trial

In addition to the usual material suggested in, e.g., ICH E9,

- A rationale for the proposed design
- Detailed description of monitoring and adaptation plan
- Roles and responsibility of bodies responsible for implementing the adaptive design
- Prespecification of statistical methods
- Evaluation and discussion of design operating characteristics
- Data access plan

Evaluating and Reporting a Completed Trial

In addition to the usual contents of an NDA or BLA,

- All prospective plans, relevant committee charters, supporting documentation as described in previous slides
- Information on compliance with adaptation plan
- Records of deliberations and participants for any interim discussions related to adaptations
- Results of interim analyses or other analyses used for adaptation decisions
- Appropriate reporting of adaptive design and its results in Section 14 of labeling
  - Effect estimates should take design into account
  - Naïve estimates (when necessary) should be accompanied by appropriate caveats

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Public Comments

- Most comments included in comprehensive responses from industry or government groups
- Two major themes:
  - People would like more guidance on Bayesian adaptive designs (and on Bayes in general)
  - Emphasis on pre-specification may read stronger than it was intended to
- Many other minor comments

Next Steps

- FDA adaptive design working group meeting regularly and consulting with subject matter experts to respond to comments
- Final version of guidance hopefully published soon
- Related draft Guidance *Interacting with the FDA on Complex Innovative Trials Designs for Drugs and Biological Products*
  - https://www.fda.gov/media/130897/download
- On the horizon: a new ICH topic (E20) on adaptive designs

Acknowledgements

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Thank you!