Updated draft FDA Guidance on Adaptive Design

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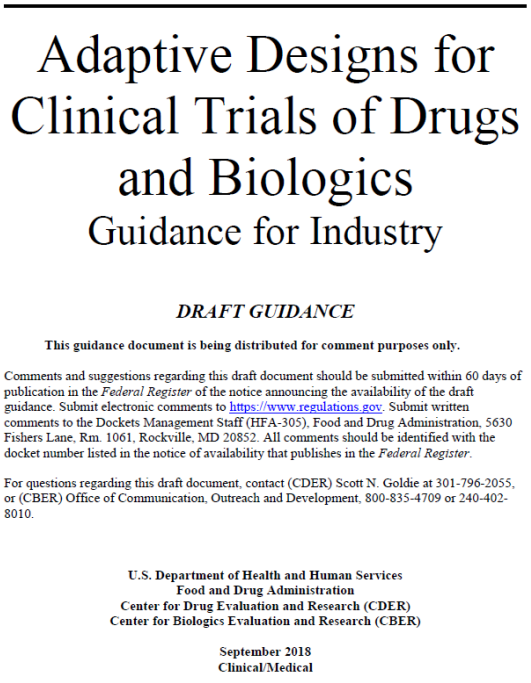
Agenda

- Background and Terminology
- Updated draft FDA guidance
  - Section II: Description and Motivation
  - Section III: Principles
  - Sections IV / V: ADs on Comparative / Noncomparative Data
  - Section VI: Special Considerations
  - Section VII: Maintaining Trial Integrity
  - Section VIII: Regulatory Considerations
- Outlook: ICH E20

Background: Regulatory Guidance

- EMA issued final Reflection Paper on Methodological Issues in Confirmatory Clinical Trials Planned with an Adaptive Design (October 2007)
- US Food and Drug Administration (FDA) issued draft guidance on adaptive design in February 2010
  - 50-pages, fairly detailed
- Draft guidance was not finalized, but updated, on 28 September 2018



Adaptive Designs for Clinical Trials of Drugs and Biologics

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Scott N. Goldie at 301-796-2055, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

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)

September 2018
Clinical/Medical

Terminology

- Adaptive designs based on *comparative / non-comparative data* replaces previously used *unblinded / blinded analyses*
- Distinction between *well understood* and *less well understood* adaptive designs no longer used

Section II: Description of and Motivation for Adaptive Designs

Definition

- An adaptive design is defined as 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 trial.

- Definition from previous draft:

  (…) an adaptive design clinical study is defined as a study that includes a prospectively planned opportunity for modification of one or more specified aspects of the study design *and hypotheses* based on *analysis of data (usually interim data)* from subjects in the study.

Advantages over non-adaptive designs

Promoting Statistical Insight

Statistical Efficiency	+ Greater statistical power + Same statistical power with smaller sample size or shorter time
Ethical Considerations	+ E.g. ability to stop a trial early if trial is unlikely to demonstrate effectiveness and can reduce number of patients exposed to unnecessary risk

Generalizability and Improved Understanding of Drug Effects	+ Possibility to answer broader questions
	  + Adaptive enrichment design
	  + Design with adaptive dose selection

Acceptability to Stakeholders	+ Added flexibility is more acceptable to stakeholders, e.g. sponsors or patients

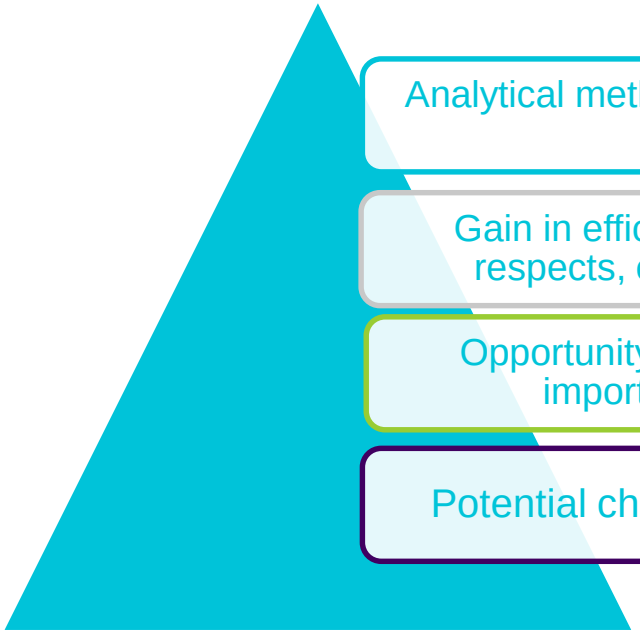
Motivation and Examples

Promoting Statistical Insight

Head Injury Trial – Bolland et al. 1998	• Interim analysis was prespecified based on pooled, non-comparative data and ultimately led to a sample size increase from 400 to 450 patients
Chronic Heart Failure Trial - PARADIGM-HF	• Addition of interim analyses with stopping rules for efficacy reduced expected sample size and expected trial duration while maintaining a similar probability of trial success
HPV Vaccine Trial – Chen et al. 2015	• Interim analysis was carried out to select one of three dose formulations to select an appropriate dose and confirm safety and effectiveness timely
Prostate Cancer Trial - STAMPEDE	• Use of a common control group, along with sequential analyses to potentially terminate treatment arms, allowed simultaneous evaluation of several treatments more efficiently
Ebola virus trial - PREVAIL II	• Trial utilized a novel Bayesian adaptive design for effectiveness decision rules and allowed potential to add experimental agents as new treatment arms and potential to supplement or replace current SOC arm

Adaptive Design Limitations

Promoting Statistical Insight



- Analytical method requirement to avoid increasing the chance of erroneous conclusions and introducing estimation bias
- Gain in efficiencies in some respects may be offset by losses in other respects, e.g. increased maximum sample size, lead time increase
- Opportunity for efficiency gains through adaptation may be limited by important scientific constraints or in certain clinical settings
- Potential challenges in interpretability and generalizability of results

Section III:
Principles for Adaptive Designs

Principles for Adaptive Designs I

Promoting Statistical Insight

Controlling the Chance of Erroneous Conclusions

- Type I error rate control can be achieved through:
  - Use of statistical theory to derive appropriate boundaries (eg for Group Sequential Designs)
  - Showing that interim analysis has negligible effect (eg for sample size re-estimations based on non-comparative results)
  - Simulations (eg for many Bayesian adaptive designs)

Estimating Treatment Effect

- End-of-trial treatment effect estimate might be biased without taking adaptation into account
  - *Adaptive designs with known methods to adjust estimate bias should plan and use such methods*

Principles for Adaptive Designs II

Promoting Statistical Insight

Trial Planning

- Adaptive design details are completely specified prior to initiation of the trial:
  - Number and timing of interim analyses
  - Type of adaptation
  - Statistical inferential methods
  - Decision rules

Maintaining Trial Conduct and Integrity

- Knowledge of accumulating data can affect trial conduct
- Limit access to interim analysis results to individuals independent of trial conduct

Section IV : Adaptive Designs Based on Non-Comparative Data

Adequately prespecified adaptations based on non-comparative data have a negligible effect on the Type I error rate

Sections V : Adaptive Designs Based on Comparative Data

General point & GSDs

- General points:
  - Generally Type I error probability is increased and treatment effect estimates are biased
  - Statistical methods should take into account adaptive trial design
  - Choice of scale (eg p-value, conditional probability) for stopping / adaptation rules is unimportant as long as operating characteristics are adequately evaluated
- Group Sequential Designs (efficacy or futility stopping):
  - Use of binding futility OK only if stopping rules are followed (otherwise Type I error probability is not controlled)
  - Conventional estimates biased towards greater effect and confidence intervals don't have nominal coverage probabilities
  - Methods available to overcome that (eg Jennison & Turnbull 1999, which is implemented in SAS PROC SEQTEST)

Sample Size Adaptation

- Without proper adjustment Type I error rate is inflated
- Pre-specification required for:
  - Hypothesis testing method
  - Rule for sample size modification
- Commonly used approach: maintaining conditional power
  - Caution: Revised sample size allows back-calculation of interim estimate
  - In order to maintain trial integrity, personnel who know revised sample size should be limited

Patient Population Adaptation (eg Enrichment)

- Enrichment designs often involve:
  - Modification of design features based on interim results and
  - Hypothesis tests in multiple populations
- Statistical methodology needs to account for both sources of multiplicity (eg Wassmer & Brannath 2016)
- Adaptive enrichment should be motivated by results from previous trials and/or strong biologic plausibility
- If baseline characteristic thought to affect treatment effect is not binary, then threshold needs to be justified appropriately
- Extent to which trial should investigate complimentary subpopulations depends on several factors (eg potential for off-label use)

Treatment Arm Selection Adaptation

- Options:
  - Adding or terminating treatment arms
  - CRM design to estimate MTD
  - Change randomisation ratio for treatment arms
- “Seamless designs that incorporate both dose selection and confirmation of efficacy of a selected dose (based on data from the entire trial) can be considered if the principles outlined in section III are followed”
- Special case: platform trial comparing treatments (often against a common control)
  - Require extensive discussion between all stakeholders and FDA

Patient Allocation Adaptation

- Covariate adaptive treatment assignment:
  - Aim: minimise differences between treatment groups on potentially prognostic covariates
- Response Adaptive Randomization (RAR):
  - Statistical, ethical, and pragmatic advantages
    - Can minimize variance of test statistics, leading to shorter trials, smaller sample sizes, and/or greater statistical power
    - Can lead to more trial subjects assigned to more promising treatments
  - RAR alone does not generally increase Type I error probability when used with appropriate statistical analysis techniques
  - Works best in trials with relatively short-term outcomes

Other adaptations

- Adaptation to Endpoint Selection
  - May be motivated by uncertainty about treatment effect sizes on multiple patient outcomes that would be considered acceptable primary endpoints
  - Statistical hypothesis testing methods should account for adaptive endpoint selection
  - Early discussion with FDA review division is recommended
- Adaptation to Multiple Design Features
  - Two or more adaptive design features can be combined
  - Same general principles apply to these complex designs
  - Type I error I probability and other operating characteristics may be difficult to estimate then
  - Clinical trial simulations (section VI.A) will often be necessary

Section VI:
Special Considerations and Topics

Simulations

- Estimate trial operating characteristics under various scenarios
  - Estimate Type I error rate under different assumptions about nuisance parameters
    - Determine limited set of scenarios on grid of plausible values (eg mortality rates of 75, 80, 85, 90, 95 and 99%)
    - If Type I error rate control achieved at the above values, then it can be assumed to be achieved for mortality rates between 75 and 99%
    - If observed value is outside the range (eg mortality rated is 50%), then additional simulations are required at end of trial
  - Estimate familywise Type I error rate with multiple endpoints
  - Considerations for precision of simulations
  - Simulations can be used to estimate power, expected sample size, length of the trial, and bias in treatment effect estimate

Section VII:
Maintaining Trial Integrity

Maintaining Trial Integrity

Promoting Statistical Insight

- Comparative interim results should be limited to individuals:
  - With relevant experience
  - Independent from personnel involved in conducting trial
- Rationale:
  - Confidence that potential unplanned design modifications are not motivated by accumulating data
  - Assurance of quality trial conduct
- Communication plan for decisions from interim analysis should be clearly outlined
- Minimize information that can be inferred by observers
- Models for implementing plan to maintain confidentiality:
  - Data Monitoring Committee
  - *Dedicated independent adaptation committee*

Section VIII: Regulatory Considerations

Regulatory Considerations

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- Interactions vary depending on stage of development and complexity of adaptive trial
- Documentation Prior to Conducting an Adaptive Trial:
  - Detailed description of the monitoring and adaptation plan
  - Roles of bodies responsible for implementing (DMC / Adaptation Committee)
  - Prespecification of statistical methods
  - Design operating characteristics
  - Simulations: incl. example trials, parameter configurations used, results, code & conclusions
  - *Written Data Access Plan defining how trial integrity will be maintained in presence of planned adaptations*
- Documentation can be included in clinical trial protocol and/or in separate documents (eg SAP, DMC charter or Adaptation Committee charter)
- Evaluating and Reporting a Completed Trial (marketing application to FDA)
  - All prospective plans, committee charters & compliance with adaptation rule
  - Records of deliberations and participants for any interim discussions
  - Results of the interim analysis

Outlook: ICH E20

Proposed Harmonisation Action:

A new guideline on the planning, conduct, and regulatory review of adaptive clinical trial designs that provides a transparent, consistent, and predictable pathway for the regulatory acceptance of results from these designs used in a global drug development program, while also providing flexibility to allow for innovative clinical trial approaches throughout the development process.

ICH harmonisation for better health

Outline of Concept Paper

Adaptive Clinical Trials

June 2018

Endorsed by the Assembly on 06 June 2018

Timelines:

- Informal Work Group was to be launched January to June 2019 to finalize the Concept Paper (but likely to be delayed until November 2019)
- Final guidance approximately 3 years after formation of ICH EWG

Issues to be Resolved

- Definitions related to adaptive clinical trials, general principles, points to consider and a review of frequently used adaptive designs
- Recommended steps to adequately plan the trial
- Opportunities for discussion and regular communication throughout development (between the sponsor and appropriate regulatory agencies)
- Regulatory criteria and fundamental statistical principles to ensure that adaptive trial provides adequate results for regulatory decision making and registration approval
- Description of opportunities for adaptive trials across the drug development process from exploratory to confirmatory phases
  - especially in regard to strategies to select the most appropriate dose and minimize exposure to ineffective doses

Thanks

Promoting Statistical Insight

- Thanks for my colleagues from Adaptive Design Working Group at PPD for their contributions to the presentation:
  - Song Wang
  - Greg Dziem
  - Rachael Song