An Overview of the FDA Draft Guidance on Adaptive Design Clinical Trials

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Adaptive Design Clinical Trials for Drugs and Biologics

DRAFT GUIDANCE

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Web link
http://insidegoogle.fda.gov/search?q=guidance+on+adaptive+design&client=InsideFDA&site=InsideFDA&lr=&proxystylesheet=InsideFDA&output=xml_no_dtd&getfields=*&x=14&y=7

Outlines of This Presentation

1. Description and motivation for adaptive designs
2. IV. General concerns
3. V. Generally well-understood adaptive designs with valid approaches to implementation
4. VIII. Safety considerations in adaptive design trials

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5. VI. Adaptive study designs whose properties are less well understood (less regulatory experience)
6. VII. Statistical considerations for less well understood adaptive design methods
7. IX. Content of an adaptive design protocol
This draft guidance represents the Food and Drug Administration's current thinking on this topic.

The purpose of this guidance is to provide sponsors and the review staff in CDER and CBER with information regarding Adaptive Design Trials (ADT) when used in drug development programs.

The term “drug” as used in this guidance refers to chemical or biological products regulated by FDA’s Center for Drug Evaluation and Research and Center for Biological Evaluation and Research.
Interest in the possibility that clinical trials can be designed with “adaptive” features, changes in design or analyses guided by examination of the accumulated data at an interim point in the trial

May lead to the studies more efficiently to provide the same information (shorter duration, fewer patients), more likely to demonstrate an effect of the drug (if one exists), more informative on the treatment’s effects (broader and better dose-response information, subgroup effects), which may lead to more efficient subsequent studies.
Setting of **adequate and well-controlled (A&WC)** [confirmatory ?] studies intended to support marketing of a drug.

Regulatory impact:
- increased rates of false positive study results (increased Type I error rate)
- introduction of (operational and statistical) biases for the estimate of treatment effect deviate from its true value

Many adaptive methods are also applicable to exploratory studies.
Definition: 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.

Analyses of the accumulating study data at prospectively planned time-points within the study may be performed in a fully *blinded* manner (comparative analyses of study endpoints or outcomes potentially correlated with these endpoints) or in a *non-blinded* manner (study endpoint data, discontinuation rates, baseline characteristics) and occur *with or without* formal statistical hypothesis testing.
2. IV. General Concerns Associated with Using Adaptive Design in Drug Development

A. potential to increase the chance of erroneous positive conclusions and of positive study results that are difficult to interpret
A. potential for counterproductive impacts of adaptive design
B. complex adaptive designs — potential for increased planning and more advanced time frame for planning
C. adaptive design in exploratory studies
D. study design changes that are not considered adaptive design
2. IV. General Concerns

A. Potential to increase the chance of erroneous positive conclusions and of positive study results that are difficult to interpret

1) Bias associated with multiplicity of options
   Choices made from among multiple candidates (doses, population subsets, endpoints) after the study begins and at one or multiple time points during the study

2) Difficulties of interpretation when a treatment effect is shown
   Select the best observed interim treatment effect among the options (especially when this occurs multiple times within a study)
   Change the nature or type of data used in the primary analysis (changing the endpoint or study population between study stages)

3) Operational Bias
   Access to the interim unblinded results have an effect on the study conduct or subjective decision-making during the course of the study
   The role of managing study conduct and addressing unexpected study issues is a responsibility that is separate and distinct from the role a DMC will have if used to implement a prospective adaptation plan.
2. IV. General Concerns

B. potential for counterproductive impacts

1) The potential to limit identifying gaps in knowledge
2) The elimination of time to thoughtfully explore study results

An often overlooked value of the time period between studies is the opportunity to thoughtfully examine the data
2. IV. General Concerns

C. complex adaptive designs — potential for increased planning and more advanced time frame for planning

D. adaptive design in exploratory studies

1) The use of adaptive designs in early development studies to learn about various aspects of dosing, exposure, differential patient response, response modifiers, or biomarker responses offers sponsors opportunities that can improve later studies.

2) Although the rigor needed is less for exploratory studies than for Adequate and Well-Controlled studies, the inflation of statistical Type I error rate or other biased estimates in the results of exploratory studies, when unrecognized, can lead to counterproductive design decisions for subsequent studies.
2. IV. General Concerns

E. study design changes that are not considered adaptive design

1) Revisions after unplanned findings in an interim analysis

2) Revisions based on information from a study-external source

   Reactive Revision: there may be unexpected safety information arising from a different study (perhaps in a different patient population), new information regarding the disease pathophysiology or patient characterization that identifies disease sub-types, new information on pharmacokinetics or pharmacodynamic responses to the drug, or other information that would have led to a different study design had the information been known when the ongoing study was designed.
3. V. Generally well-understood adaptive designs with valid approaches to implementation

A. Adaptation of study eligibility criteria based on analyses of pretreatment (baseline) data
B. Adaptations to maintain study power based on blinded interim analyses of aggregate data
C. Adaptations based on interim results of an outcome unrelated to efficacy
D. Adaptations using group sequential methods and unblinded analyses for early study termination because of either lack of benefit or demonstrated efficacy (ICH E9)
E. Adaptations in the data analysis plan not dependent on within study, between-group outcome differences
3. V. Generally *well-understood* adaptive designs with *valid approaches* to implementation

A. Adaptation of study eligibility criteria based on analyses of pretreatment (baseline) data

1) Examination of baseline characteristics of the accumulating study population may show that the expected population is not being enrolled and that by modifying eligibility criteria subsequent subject enrollment may be shifted towards a population with greater numbers of patients with the desired characteristics.

2) Such examination of baseline information and modification of study eligibility criteria can contribute to timely completion of informative studies.

3) Knowledge of the baseline characteristics of the overall study population at any time during the study does not generate concerns of introducing statistical bias as long as the treatment assignment remains *blinded*. 
3. V. Generally *well-understood* adaptive designs with *valid approaches* to implementation

B. Adaptations to maintain *study power* based on *blinded interim analyses* of aggregate data

1) The estimated power of a study to detect a treatment effect is dependent upon (a) the study *sample size*, (b) the targeted (assumed actual or minimum acceptable) treatment *effect size*, and (c) the assumed population *variance* of the patient measure being studied or the expected control group event rate for event-driven studies.

2) Examining the data in this *blinded* analysis does not introduce bias, and no statistical adjustments are required, as it does not contain any information potentially revealing the between group differences.

3) Decisions to increase the sample size are made in this manner.

4) Decreasing sample size is not advisable due to the chance of making a poor choice because of the high variability of the effect size and event rate or variance estimates early in the study.
3. V. Generally well-understood adaptive designs with valid approaches to implementation

C. Adaptations based on interim results of an outcome unrelated to efficacy

1) Look for serious adverse events at an interim stage of the study and discontinue a dose group with unacceptable observed toxicity.
2) This approach may be undesirable if there might be greater effectiveness associated with the more toxic dose that could outweigh the increased toxicity in a risk-benefit comparison.
3) If there are no efficacy-related interim analyses performed, the interpretability of the final study result is not impaired by concerns of statistical bias or operational bias in study conduct.
3. V. Generally *well-understood* adaptive designs with *valid approaches* to implementation

D. Adaptations using *group sequential methods* and *unblinded analyses* for early study termination because of either lack of benefit or demonstrated efficacy (ICH E9)

1) Developed group sequential statistical design and analysis methods allow valid analyses of interim data and provide well recognized alpha spending approaches to address the control of the Type I error rate (e.g., O’Brien-Fleming, Lan-DeMets, Peto methods) to terminate a study early when either no beneficial treatment effect is seen or a statistically robust demonstration of efficacy is observed.

2) An independent, non-sponsor controlled, Data Monitoring Committee is an inherent part of the group sequential method’s protection of study integrity. Group sequential monitoring are discussed in the ICH E9 guideline “Statistical Principles for Clinical Trials” (sections 3.4, 4.1, 4.5).
3. V. Generally well-understood adaptive designs with valid approaches to implementation

E. Adaptations in the data analysis plan not dependent on within study, between-group outcome differences

1) (ICH E9) After a blinded inspection of the data violate prospective assumptions regarding the distribution of the data, the Statistical Analysis Plan (SAP) may be updated regarding the appropriate data transformations, adding covariates identified from other research sources, or reconsideration of parametric versus non-parametric analysis methods.

2) If the amount of missing data in the preferred outcome assessment exceeds some prospectively stated criterion, a pre-specified alternative outcome would be used as the primary efficacy endpoint.

3) if an insufficient number of events within the initial composite event endpoint were observed, an analytic plan accommodating inclusion of one or two specific additional types of events might be appropriate.
4. Safety considerations in adaptive design trials

A. Safety considerations for subjects in adaptive design dose escalation studies early in drug development

B. Safety considerations related to earlier design and conduct of adequate and Well-Controlled Studies with major expansion in the number of treatment-exposed subjects
4. Safety considerations in adaptive design trials

A. Safety considerations for subjects in adaptive design dose escalation studies early in drug development

1) Unlike to studies designed with sequential cohorts of subjects escalating the dose for each successive cohort, some adaptive design algorithms permit a change in dose level after each subject not having an unacceptable adverse response, or based upon the accumulated responses of previously enrolled subjects.

2) It may be inappropriate that an adaptive study aggressively is designed for rapidly reaching a decision on the highest tolerable dose, where there is little to no prior safety experience with a drug (or related drugs) and the known or hypothetical adverse effects may be serious.

3) Study simulations with multiple combinations of escalation criteria, dose-step size, and hypothetical assumed relationships of exposure to severity and frequency of adverse events may be useful. They may assist in assessing the risks and selecting a design that offers improved efficiency without increasing risk excessively.
4. Safety considerations in adaptive design trials

B. Safety considerations related to earlier design and conduct of adequate and Well-Controlled Studies with *major expansion* in the number of treatment-exposed subjects

1) Unlike to the drug development programs that the safety-related data of each completed study are examined prior to finalizing the design and commencing the subsequent study, adaptive design methods are sometimes intended to condense the development program into fewer fully independent studies, with more rapid advancement from small early studies into the large Adequate and Well-Controlled (A&WC) studies.

2) This may lead to have only a limited amount of safety data available when a large adaptive study is being planned that will entail a great increase in the number of patients exposed to the drug.

3) Increasing the safety data monitoring (more frequent and extensive assessment) may not resolve this concern fully, it may be necessary to enroll limited numbers of patients until sufficient safety data are accumulated and examined to support expansion of the study to larger numbers of patients.
Guidance for Industry
Adaptive Design Clinical Trials
for Drugs and Biologics (draft)

Part 2
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CBER/OBE/DE/TEB
MPCC, April 6, 2010
Section VI: Less Well Understood Design

- Relatively little regulatory experience and whose properties are not fully understood at this time.
- Adaptation based on unblinded interim analyses.
Section VI: Topics

- Dose Selection
- Relative Treatment Group Responses
- Sample Size based on Interim-Effect Size
- Patient Population Based on Treatment-effect
- Endpoint Selection
- Multiple-Study Design Features
- Non-Inferiority Studies
VI: Dose Selection Studies

- Objective: Select effective and safe dose
- Begin study with multiple doses
- Adaptively drop or add dose groups, based on clinical endpoint or a biomarker
- Adjust sample size of the experiment or individual dose group
- Provides flexibility with prospectively planned study
VI: Dose Selection (cont)

• With rigorous protection of the Type I error rate, a highly flexible design can be used.
• In some cases, biomarker or a surrogate endpoint can be used for dose selection. However, one need to take into account the relationship between the biomarker and the ultimate endpoint.
VI: Adaptive Randomization

- Outcome dependent randomization or play the winner approach.
- Randomization process changes continuously dependent upon the outcome.
- Limitation: Availability of response soon after the exposure to treatment.
- Usually used to allocate more subjects to treatment than placebo.
VI: Adaptive Randomization (cont)

• Can be used in dose response designs by allocating fewer subjects to doses that appear to have a low probability of success.

• More useful for exploratory studies where estimation is the objective instead of hypothesis testing.

• Results are not as easily interpretable.
VI: Adaptive Randomization (cont)

- Outcome based randomization constantly changes probability of randomization over the course of the study.
- It raises a concern regarding the balance of patient characteristics among the treatment groups.
- It could lead to poor dose selection.
VI: Adaptive Randomization (cont)

- Recommendation: Maintain sufficient number of patients in the placebo group.
- It also will maintain the power of the study.
- Estimates from this type of study should be used conservatively in setting the sample size of a subsequent study.
VI: Adaptation of Sample Size based on Interim-Effect Size

• This is most common scenario.
• There is no perfect estimate of treatment effect for the proposed study population.
• This can be accomplished based on blinded interim analyses.
• Sample size is increased based on the knowledge of smaller effect size (still clinically relevant) than had been anticipated.
• Some adaptation affect the power of the study that would require re-estimation of sample size.
VI: Adaptation of Sample Size based on Interim-Effect Size (cont)

• These methods should be used to increase the sample size, not for decrease.
• Decrease in sample size is best achieved by group sequential designs where a well-understood alpha spending rules are applied and decrease in sample size occurs by early termination at the time of the interim analysis.
VI: Adaptation of Sample Size based on Interim-Effect Size (cont)

- Use of an *unblinded* analysis can lead to increase in Type I error rate.
- To adjust for this, alpha level for the final analysis needs to be modified.
- An alternative is to weigh the data from the successive portions unequally. Weights should be pre-defined.
- Not seen used in practice due to subjectivity of the weights and then interpretation of the results.
VI: Adaptation of Patient Population Based on Treatment Effect.

• Also called ‘enrichment designs’.
• Sometimes can improve power of the study if based on blinded analysis.
• Sometimes it is based on a biomarker.
• Adaptive methods can be used to select an optimum dose and/or a subset.
• However, bias may be introduced and may require adjustment to Type I error rate.
VI: Adaptation of Endpoint Selection Based on Treatment Effect.

- Generally, it should be determined at an early stage and should be based on clinical benefit.
- In some cases, when drug’s effect is not well understood, a change in the primary endpoint may be necessary.
- Requires appropriate statistical control of Type I error rate for multiplicity of endpoints selection.
VI: Adaptation of Endpoint Selection Based on Treatment Effect (cont).

- Endpoint modification needs to be prospectively planned and should be clinically appropriate.
- Quality of data on each endpoint should not be based on their possibility of selection.
- A lower quality data can lead to misleading effect size and could be a counterproductive change in the endpoint.
VI: Adaptation of Multiple-Study Design Features

- The study design should prospectively account for the multiple adaptation and maintain control of the study-wide Type I error rate.
- Adaptation could include multiple design features as discussed before.
- However, complexity of adaptation will increase difficulty in interpreting the study results.
- Therefore, *number of adaptations should be limited.*
Section VII:
Statistical Considerations for Less-Understood AD methods

- Control of Type I error
- Biased Treatment Effect
- Increased Type II Error rate (decreased Power)
- Simulation
- Prospective Analysis Plan
VII: Controlling Study-wide Type I Error Rate

• At each adaptation, there is an increase in Type I error.
• This is due to increase in opportunities for early rejection of null hypotheses.
• Controlling Type I error is best accomplished by prospectively specifying all possible adaptation plans and applying appropriate statistical methodology.
VII: Controlling Study-wide Type I Error Rate (cont.)

• Multiple adaptation is a challenge in controlling Type I error and should be addressed at the protocol design stage.
• Adaptations not envisioned at the protocol design stage should be limited in scope and must be of particular importance,
• It is easy to introduce statistical bias if modifications are made based on interim analyses.
• Increase in sample size is commonly used based on interim analyses.
VII: Controlling Study-wide Type I Error Rate (cont.)

- Increase in sample size is to increase power based on observed unbiased treatment effect.
- Increase in sample size does not eliminate the bias in the treatment effect. Instead, a sample size increase can result in the bias increasing the Type I error more than would occur without the sample size increase.
- Impact of small biases can be magnified when sample size increases are enabled.
VII: Statistical Bias in Estimates of Treatment effect

- Treatment effect when based on small samples at an interim analysis have potential to overstate the true effect size.
- This can lead to selecting a wrong adaptation choice and thus miss detecting a true treatment effect (Type II error)
VII: Statistical Bias in Estimates of Treatment effect (cont)

• If the treatment effects differ substantially before and after of a particular adaptation, it could be a major concern.

• It makes the overall treatment effect estimate difficult to interpret.
VII: Potential for Increased Type II Error Rate

- Need to avoid increase in Type II Error (false negative)
- It could happen due to insufficient power to detect a real treatment effect
- Dose selection, if not appropriately conducted, can decrease power.
- Liberal futility stopping criterion may increase Type II error rate.
VII: Role of Clinical Trial Simulation

- With multiple adaptation in a trial, complexity of the design increases.
- Trial simulation can help by introducing real life scenarios in the design and observing statistical properties of the study.
- Some of these adaptations and simulation can lead to a Bayesian approach where different prior distributions can be evaluated for their suitability.
VII: Role of Clinical Trial Simulation (cont)

- Trial simulations can also be helpful in comparing the performance characteristics among several competing designs under different scenarios.
- It will help to compare the probability of success of the trial for the objective.
- Due to complexity of adaptation, modeling simulation provide a solution for demonstrating control of the Type I error rate.
- Generally, an analytical solution is not available for these adaptation procedures.
VII: Prospective Statistical Analysis Plan

- Prospective SAP is more important for trials based on adaptive procedures.
- It should be available by the time a protocol is finalized.
- SAP should include: planned changes, statistical methods to implement adaptation, data analysis procedure for each stage of adaptation, and justification for the method of control of Type I error rate.
VII: Prospective Statistical Analysis Plan (cont)

- SAP are generally more detailed and complex than for standard clinical trials.
- A modification to such a SAP should be discouraged.
- If necessary, modification to SAP should occur before any unblinded analyses are performed.
- A blinded steering committee can make such protocol and SAP changes.
- There needs to be a firewall between the personnel with access to the unblinded analyses and those personnel making the SAP changes.
XI: Contents of an AD Protocol

• The guidance provides details of necessary documentation and practices to protect study blinding and information sharing for adaptive designs. It includes:

• Detail documentation about adaptation features and its possible impact, computer simulations with all assumptions utilized, computer programs used for simulation, any analytical derivations, written agreement about the data sharing firewall.
X: Interactions with FDA

- Expects early and multiple interactions with FDA.
- AD not suitable for special protocol assessment (SPA)
That is all !!
Thanks for your time and listening!

Clarifications and Questions