Interacting with the FDA on Complex Innovative Trial Designs for Drugs and Biological Products

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Draft Guidance for Industry

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Center for Biologics Evaluation and Research
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Interacting with the FDA on Complex Innovative Clinical Trial Designs For Drugs and Biological Products

Draft Guidance for Industry

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This document provides guidance to sponsors and applicants on interacting with the FDA on complex innovative trial design (CID) proposals for drugs or biological products.[1] FDA is issuing this guidance to satisfy, in part, a mandate under section 3021 of the 21st Century Cures Act (Cures Act). In accordance with the Cures Act mandate, this guidance discusses the use of novel trial designs in the development and regulatory review of drugs and biological products, how sponsors may obtain feedback on technical issues related to modeling and simulation, and the types of quantitative and qualitative information that should be submitted for review. Additional recommendations related to FDA's mandates under section 3021 of the Cures Act are addressed in FDA's draft guidance on Adaptive Designs for Clinical Trials of Drugs and Biologics (Ref. 1).[2]

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required.

[1] The term *drug* as used in this guidance refers to both human drugs and biological products unless otherwise specified.

[2] See also guidance for industry *Enrichment Strategies for Clinical Trials to Support Determination of Effectiveness of Human Drugs and Biological Products* (March 2019). We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs or Biologics guidance web pages at https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs, https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances

II. SCOPE

Although CID has been referred to as complex adaptive, Bayesian, and other novel clinical trial designs, there is no fixed definition of CID because what is considered innovative or novel can change over time. For the purposes of this guidance, CID includes trial designs that have rarely or never been used to date to provide substantial evidence of effectiveness in new drug applications or biologics license applications. A common feature of many CIDs is the need for simulations rather than mathematical formulae to estimate trial operating characteristics (Section III of this guidance). Some examples of trial designs that might be considered novel or CID are those that formally borrow external or historical information or borrow control arm data from previous studies to expand upon concurrent controls (Section IV of this guidance), Sequential Multiple Assignment Randomized Trials (Section IV), or master protocols.

The primary focus of this guidance is on FDA and sponsor interactions for CID proposals for trials intended to provide substantial evidence of effectiveness. In most cases, interactions related to CID proposals will occur in the context of investigational new drug applications (INDs) or Pre-IND meetings. Novel clinical trial designs call for clear communication between sponsors and FDA on aspects of the design, including the purpose, execution, and operating characteristics (such as the chance of producing erroneous conclusions) of the design, and how the trial data will be analyzed and presented. This guidance provides recommendations for such interaction. The guidance also provides examples of clinical trial designs that FDA would consider to be CID and describes the type of information FDA recommends submitting with the proposals to facilitate a productive discussion between sponsors and FDA. Additionally, the guidance addresses the role of simulations in clinical trial design and planning.

This guidance does not indicate whether specific novel designs are or are not appropriate for regulatory use, as such determinations will be made on a case-by-case basis depending on the reasons the design is being proposed, its validity in the specific setting, and possibly on factors unique to a given development program. A CID proposal that may be appropriate for one product class in one indication may not be appropriate for another product class or in another indication. The emphasis in this guidance is on the necessary elements for effective interactions between sponsors and FDA regarding CID proposals.

III. INTERACTING WITH FDA ON CID PROPOSALS

A. Meeting Availability

Because CID proposals may involve novel scientific review considerations, FDA encourages sponsors of CID proposals to seek early interaction with FDA regarding details of their CID plans. In general, sponsors should use existing pathways for interacting with FDA during the course of the clinical development program, including Type A, Type B, Type B end-of-phase, and Type C meetings, IND amendment review, and possibly pre-IND meetings for early-phase studies with novel design elements (Ref. 2). FDA's review of CID proposals often involves challenging evaluations of design operating characteristics, including extensive computer simulations, as well as detailed

discussions across disciplines and FDA offices. This may make it difficult for FDA to adequately review such designs under short timelines.

Where the CID proposal involves extensive computer simulations to determine important aspects of the design, FDA may grant additional Type C meetings to provide more detailed feedback, especially when the product is being investigated to fulfill an unmet medical need or treat a serious or life-threatening condition. Sponsors are encouraged to indicate within meeting packages how the CID proposal fits into the overall clinical development program and in what ways it may improve the efficiency of the study or the generalizability of its results compared to a simpler or conventional clinical trial design.

Sponsors may also consider FDA's pilot program for complex innovative trial designs (CID Pilot Program) to obtain additional meetings with FDA review disciplines on their proposed CID (Ref. 3). The CID Pilot Program provides sponsors with additional opportunities to meet with FDA about their CID proposal and to obtain detailed feedback from review teams and senior regulatory decision-makers. The program will run from August 30, 2018, through September 30, 2022, and is intended to advance the use of CIDs. More details about applying to participate in the CID Pilot Program and program requirements are available on FDA's webpage (Ref. 4).

B. Common Elements of CID Proposals To Be Submitted For Review

Detailed documentation is necessary for FDA to review novel design proposals thoroughly and provide feedback. Documentation should include the novel features that are planned to be incorporated, the timing and details of the planned implementation, and how the design addresses the underlying scientific objectives. The specific documentation needed will depend on the type of proposal submitted, but there are certain elements that will be common to most proposals. In this section, we give examples of common elements that should be included in a CID proposal, whenever applicable. In Section IV of this guidance, we give examples of additional information that may be needed for specific types of CID proposals.

- A discussion of the statistical analysis considerations related to the complex innovative design features.
- A discussion of the choice of trial design and how it fits into the overall drug development plan. It is often helpful to explain how the novel design provides advantages over conventional trial designs for the particular product and indication.
- A detailed description of important aspects of the design, including plans for any possible adaptations, implementation details for interim analyses, and any unique or novel decision criteria.
- If prior information is being used, details about the source and choice of the prior information, its relevance to the proposed trial design, and an explanation of steps taken to ensure that all relevant prior information is accounted for, so that the prior information does not lead to misleading results.

- When external information is explicitly borrowed into a design, such as in a Bayesian framework, a rationale for the borrowing and an explanation of how the prior distribution was formed from the prior information.
- A detailed evaluation of the operating characteristics of the design, including its chance of producing erroneous conclusions and the reliability of treatment effect estimates. Type I error probability control and power should be addressed where applicable.
- For Bayesian inference, appropriate alternative trial characteristics should be considered, such as the maximum posterior probability of the null across values of the test statistic in the rejection region or the maximum posterior probability of a minimally clinically significant treatment effect across values of the test statistic outside of the rejection region (Ref. 5). It is also often informative to assess the sensitivity of trial operating characteristics to the choice of a prior distribution.
- A simulation report if simulations are used to evaluate study operating characteristics.
- Relevant instructions that will be provided to a Data Monitoring Committee, adaptation committee, or other body charged with implementing critical aspects of the CID, as applicable and necessary to understand the design.
- A comprehensive data access plan defining how trial integrity will be maintained. This is discussed in detail in FDA's draft Guidance for Industry on Adaptive Designs for Clinical Trials of Drugs and Biologics (Ref. 1).
- For any trial that uses patient input to inform the choice of endpoints, acceptable benefit-risk trade-offs, minimum acceptable benefit, maximum acceptable risk, or the level of certainty that will be targeted for estimates of treatment effects on safety and effectiveness, a study protocol for any study used to evaluate patient preferences should be submitted for discussion (Ref. 7).

C. Bayesian Features of CID Proposals

Bayesian approaches may be well-suited for some CID settings because they can provide flexibility in the design and analysis of a trial, particularly when complex adaptations and predictive models are used. In addition, Bayesian inference may be used in settings where it is advantageous to combine multiple sources of evidence, such as extrapolation from adult data to pediatric populations, or to borrow control data from Phase 2 trials to augment a Phase 3 trial (see Section IV of this guidance).

If a sponsor chooses to submit a Bayesian CID proposal, FDA's evaluation of the proposal will rely on clear communication between the sponsor and FDA regarding two areas: the prior distribution and the study decision criteria for primary and key secondary endpoints. Bayesian approaches that explicitly borrow information external to a trial are not appropriate for every development program and cannot be used to avoid the requirement to provide substantial evidence of effectiveness for approval. When submitting such a proposal, sponsors should include a rationale for the borrowing. As the

focus of this guidance is on interactions with FDA regarding CID, the following sections discuss the elements unique to a Bayesian CID needed to facilitate discussion between a sponsor and FDA.

1. Prior Distributions

Bayesian inference relies on well-informed specification of the prior distribution to control the chance of erroneous conclusions. Without careful construction of the prior, the use of Bayesian methods can increase the chance of erroneous conclusions. As such, discussions regarding the prior distribution are critical to FDA's evaluation of Bayesian proposals. Prior distributions can be formed from a variety of sources, including previous trial data or other clinical data, and they can also incorporate features such as downweighting of earlier data relative to contemporaneous data or initial skepticism regarding the likelihood of large treatment effects. In some settings, non-informative or reference prior distributions may be used to reflect a stance of general uncertainty regarding the parameters of interest.

In general, Bayesian CID proposals should include a robust discussion of the prior distribution. Any data or other external information used to form the prior distribution should be presented in detail for FDA to understand the source and completeness of the external information, its relevance, and the quality and reliability of the data. One aspect of the relevance of external data relates to the issue of exchangeability, which should be addressed in Bayesian CID proposals. The concept of exchangeability is discussed in detail in FDA's Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials (Ref. 6). In order to obtain accurate inference, informative prior distributions should generally be based on a thorough evaluation of relevant evidence, including evidence that may suggest skepticism of the existence or magnitude of a treatment effect. For this reason, a Bayesian proposal should also include a discussion explaining the steps the sponsor took to ensure information was not selectively obtained or used. In cases where downweighting or other non-data-driven features are incorporated in a prior distribution, the proposal should include a rationale for the use and magnitude of these features.

2. Decision Criteria

For many clinical studies conducted using a frequentist statistical approach, hypothesis tests at a one-sided alpha level of 0.025 are used to establish support for the efficacy of a product. When Bayesian approaches are used, it is necessary to specify alternate decision criteria. The choice of decision criteria has a large impact on both the design and the quality of inference from a study.

For example, a study protocol may state that a conclusion of effectiveness will be supported if the probability that the response rate in Group A is greater than the response rate in Group B exceeds 99% (in mathematical notation, $Pr(\pi_A > \pi_B) > .99$). Another study protocol may state that a demonstration of effectiveness

requires that the probability that the response rate in Group A is at least 10 percentage points higher than the response rate in Group B exceeds 95% ($Pr(\pi_A - \pi_B > .10) > .95$).

Sponsors should propose decision criteria in study protocols for all primary and secondary endpoints that would be included in product labeling if approved. These proposals should include a rationale for the choice of criteria. FDA will evaluate these proposals during IND review, and final determination will be based upon agreement with the review division.

For some Bayesian designs, it is possible to use simulations to estimate the frequentist operating characteristics of power and Type I error probability. Calibrating to frequentist operating characteristics in this way can provide a basis for comparing a given Bayesian proposal with previous studies or development programs that used frequentist inference, as Bayesian and frequentist inference are not otherwise generally directly comparable.

D. Simulations

A common feature of CID proposals is the use of simulations to estimate trial operating characteristics or to optimize design parameters such as number and timing of interim analyses. FDA's Guidance for Industry: Adaptive Designs for Clinical Trials of Drugs and Biologics (Ref. 1) discusses such simulations in some detail in the context of adaptive designs specifically, and provides recommendations regarding the content and format of simulation reports included with applications. The same considerations apply generally across a wide variety of CID proposals.

For studies intended to provide substantial evidence of effectiveness, it can be advantageous to discuss plans for trial simulations at meetings with FDA. Specifically, End of Phase 2 meetings often occur at a stage in the development process where preliminary plans for Phase 3 trials can be discussed, and these preliminary plans may suggest the need for trial simulations. Structuring part of the End of Phase 2 discussion around these simulations can help a sponsor and FDA consider the scenarios to be explored in simulations and the underlying trial assumptions, such as accrual rate or likely control group outcomes.

IV. EXAMPLES OF CID AND INFORMATION NEEDED TO FACILITATE INTERACTIONS

This section includes a discussion of several specific CID elements. The intent is to give examples of some of the information that will be needed for a sponsor and FDA to have a productive interaction regarding these designs in the context of a meeting or application review. The examples are not comprehensive; many other CID elements may be proposed, some of which may yet be invented. Furthermore, what is considered CID today could become routine in the future.

A. Leveraging Data From Phase 2 to Phase 3

There is considerable and growing interest in improving the efficiency of Phase 3 trials by leveraging control data from Phase 2 trials. In this scenario, outcome data from a Phase 2 trial can be incorporated in the estimation of treatment differences from a subsequent Phase 3 trial. Use of Phase 2 control data to bolster the control group in a Phase 3 trial can lead to reduction in the total Phase 3 sample size and therefore of the time and cost to complete the Phase 3 trial.

A CID proposal to incorporate Phase 2 data into Phase 3 should include a discussion of the clinical comparability of the Phase 2 and Phase 3 populations, including similarity of study procedures, treatments, and endpoints, and whether there have been any changes in standards of care of patients over time that could affect outcome. The Phase 2 data should be presented in enough detail for FDA to evaluate its quality. The proposal should include a landscape assessment to determine whether other data from other sources (for example, in the medical literature) are consistent with the Phase 2 data. For example, if the prior control group has a systematically lower response rate than the concurrent control group due to changes in care, borrowing the prior data could increase the chance of a false conclusion of effectiveness. A strategy for evaluating and addressing heterogeneity between the prior data and the concurrent Phase 3 data, such as the use of hierarchical models or other approaches that automatically downweight borrowing in the presence of heterogeneity, should be included. As discussed above, if Bayesian approaches are used, the proposal should include detailed discussions of decision criteria and prior distributions, including the effective sample size of the Phase 2 data to be borrowed and how it will be borrowed.

B. Sequential Multiple Assignment Randomized Trials (SMARTs)

Sequential Multiple Assignment Randomized Trials (SMARTs) are designed to inform the development of adaptive interventions. An adaptive intervention is a sequence of decision rules that specifies when and how the type and/or intensity of a treatment should be modified depending on the patient's characteristics and/or ongoing performance (e.g., response, adherence) to optimize clinically important outcomes. A SMART is comprised of multiple intervention stages, and each stage corresponds to one of the critical decisions involved in the adaptive intervention. In a SMART, patients move along multiple stages and are randomly assigned to one of several treatment options at each stage.

Elements that need to be discussed and communicated with FDA in SMART clinical trial proposals or similar designs include the statistical questions/hypotheses, number of stages, interventions embedded in the design, intermediate response categories, a clear illustration of the flow diagram, and methods to adjust for multiplicity if needed.

V. REFERENCES

1. Draft Guidance for Industry: Adaptive Designs for Clinical Trials of Drugs and Biologics, September 2018*, https://www.fda.gov/media/78495/download.

2. Draft Guidance for Industry: Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products, December 2017*, https://www.fda.gov/media/109951/download.

3. Food and Drug Administration, Notice, Complex Innovative Designs Pilot Meeting Program (83 FR 44274, August 30, 2018), available at: https://www.federalregister.gov/documents/2018/08/30/2018-18801/complex-innovative-designs-pilot-meeting-program.

4. Complex Innovative Trial Designs Pilot Program, available at: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm617212.htm.

5. Bryant, J. and Day, R. (2000). Comment on Lee and Zelen's Clinical Trials and Sample Size Considerations: Another Perspective. Statistical Science, 15(2), 106 - 108.

6. Guidance for Industry: Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials, February 2010, available at: https://www.fda.gov/media/71512/download.

7. Draft Guidance for Industry: Patient-Focused Drug Development: Collecting Comprehensive and Representative Input, June 2018*, https://www.fda.gov/media/113653/download.

* When finalized, this guidance will represent FDA's current thinking on this topic.