March 20, 2018

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2018-N-0049: Promoting the Use of Complex Innovative Designs in Clinical Trials

Dear Dionne Price:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments to the public meeting on Promoting the Use of Complex Innovative Designs in Clinical Trials.

BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial, and environmental biotechnology products.

BIO is fully supportive of the development and launch of this important initiative. We share FDA's goals for the pilot program to promote public learning about Innovative Clinical Trial Design (ICTD) and demonstrate the use of novel designs that will increase the efficiency and/or feasibility of clinical development.

Further, BIO believes the pilot program presents multiple opportunities for public learning and subsequent advancement of ICTD. These opportunities include: (i) learning about the status of the pilot program by understanding the types of categories of ICTD submitted and accepted to the pilot, (ii) learning about FDA's rationale for accepting or rejecting a proposal into the pilot, (iii) learning how to best prepare for and ensure a productive meeting with FDA on ICTD, and (iv) learning through case examples that are accepted into the pilot.

To further advance a successful implementation of the ICTD Pilot Program, and maximize its diverse learning opportunities, BIO has developed a series of recommendations for consideration by the Agency. Our recommendations focus on the pilot's application timelines, communication on acceptance/rejection into the pilot, and disclosure of information. These are discussed in detailed in **Appendix A**.

In addition, BIO has developed high-level case studies of innovative clinical trial designs which have historically shown low level of regulatory acceptance. These examples, discussed in detailed in **Appendix B**, include: open-label study with external control for small population; Bayesian augmented control design with a small placebo or active control for a pediatric or small population; adaptive trial to evaluate a combination of two unapproved products to treat or prevent disease with serious complications; platform trials; as well as basket trial designs.

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BIO recognizes that there might be a wide range of designs sponsors may submit to the ICTD pilot. Thus, the goal of our case studies is to provide insight into the general types of innovative clinical trial designs that BIO would like to see in the pilot program, as we believe they hold great educational value and would help advance the overall learning goal of the pilot program.

Sincerely,

/S/

Sesquile Ramon, Ph.D.
Director, Science & Regulatory Affairs
Biotechnology Innovation Organization

Appendix A.

I. Recommendations on the timing and content of a pilot application

The recommendations put forward assume the innovative study the Sponsor is proposing for the pilot program is considered to be a pivotal trial and, if positive, is expected to support an NDA/BLA submission.

The decision as to *when* in the development of a product to apply to the pilot program should be at the Sponsor's discretion. When a Sponsor has accumulated enough nonclinical and clinical evidence on a product, and they want to proceed with an innovative study design, the Sponsor may then choose to apply to the program. The details will depend on the product and context: for example, a promising molecule for a high unmet need disease could be proposed earlier in its development cycle.

The timing of the application may also depend on the complexity of the development program, a need to define new endpoints, and/or the overall risk/benefit profile of the product observed up to the time of the application to the pilot. It can be expected that the decision to grant acceptance into the pilot will be made within the context of the overall development plan of the product, including choice of endpoints and risk/benefit profile. For that reason, for products with more complex development paths, the Sponsor may want to consider aligning the timing of the request to join the pilot with the submission of the Pre-Meeting Package (PMP) for the Type B End-of-Phase (EoP) meeting and propose that the first dedicated statistical review meeting take place after the Type B (EoP) meeting. For products with less complex development paths, the request to join the pilot could be submitted prior to the request for the Type B (EoP) meeting with a proposal that the first dedicated statistical review meeting take place before the type B (EoP) meeting. In general, we believe the process should strive to achieve a finalized protocol in the most time efficient manner.

The timing of the statistical review meetings could be negotiated between FDA and the sponsor with the expectation that the first meeting could take place 30-45 days after the acceptance into the pilot. The proposal for 120 days between the two dedicated meetings seems reasonable for trials with complex (*e.g.,* simulation) components; for simpler designs a potentially shorter time interval (*e.g.,* 30-90 days) could be mutually agreed upon between the Agency and the Sponsor. To help streamline the second statistical review meeting, the FDA could commit to providing to the Sponsor written comments related to their evaluation of the design, one (1) month before the second statistical review meeting. If the timing between the meetings is agreed to be shorter, (*e.g.,* 30-90 days for less complex proposals), then the FDA could commit to providing written comments 15 days or less, prior to the second review meeting (timing of the comments, would be negotiated together with timing of the second meeting).

Overall, applying for the pilot a month or two before the submission of the request for the Type B (EoP) meeting can be advantageous to the Sponsor, as this should allow study protocol finalization within 2-4 months of the Type B (EoP) meeting. Pilot applications submitted in conjunction with, or a few days after, the PMP submission may, in some instances, be perceived as having a negative impact on the overall project timelines; with two statistical meetings 120 days apart, study protocol may not be finalized until 1-7 months after the Type B (EoP) meeting. We encourage the Agency to keep flexibility in its

meeting timelines, particularly in circumstances where protocol finalization could be achieved in shorter timeframes.

Similarly, as with the timing of the application, the content of the application and meeting materials will vary, depending on the complexity of the program and/or complexity of the statistical design, and will also depend on the timing of the EoP PMP submission.

Based on the points discussed above, BIO recommends FDA consider the pilot submission and review timelines presented in Figure 1. In addition, recommendations on submission and review timelines, together with the content of submission/meeting materials, are summarized in Table 1.

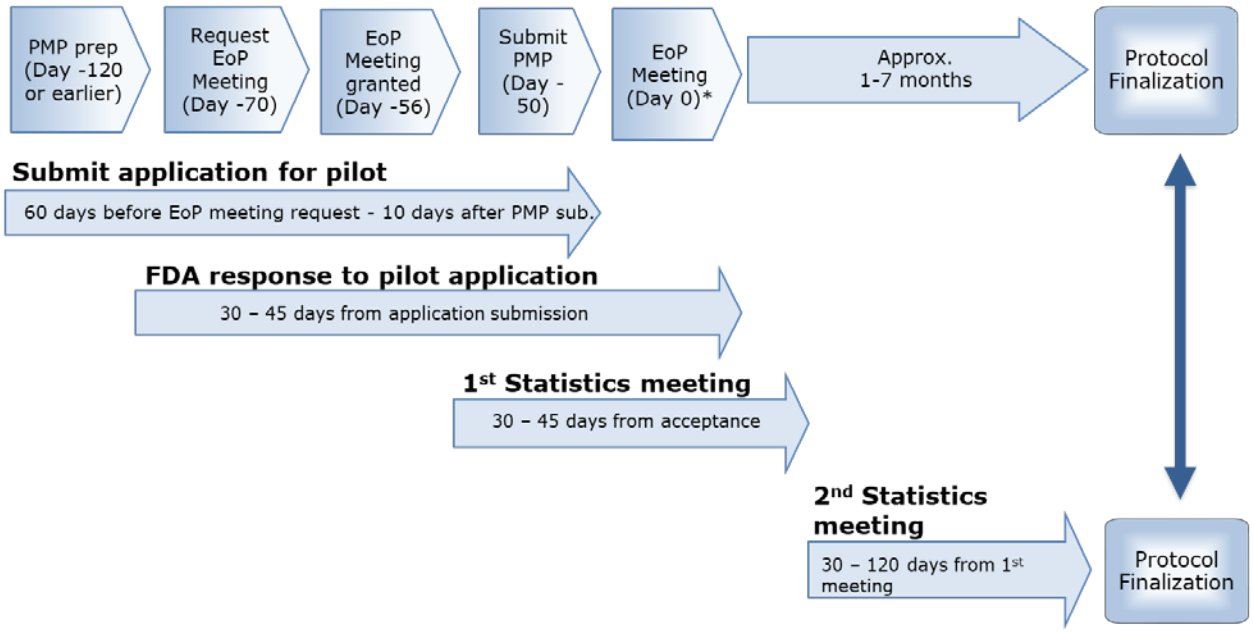

Figure 1. Pilot Submission and Review Timelines. Principle: fit the pilot process timelines within existing End-of-Phase (EoP) Type B meeting processes. (* For the purpose of these timelines, Day 0 is the day proposed by the Sponsor and not the actual day of the meeting.)

Table 1. Timelines and content of submission packages/meeting materials for the FDA pilot on Innovative Clinical Trial designs.

Event	Recommendations
Request to join the pilot – submission timeline	Depending on the overall development strategy, the sponsor may decide to apply to the pilot before or after the PMP package was submitted: *E.g.* 60-45 days **before** submitting a request for a Type B (EoP) meeting, with an intention to hold the first statistical review meeting prior to the Type B meeting.

	E.g. 0-10 days **after** the PMP package for the Type B meeting is submitted, with the intention to hold the first statistical review meeting ~30 days after the Type B meeting.
Request to join the pilot – submission materials	For pilot requests submitted after the PMP package submission, the Sponsor may utilize a summary of the PMP materials and/or reference the PMP package. Regardless, the application should include description of the development plan, information about the disease and target population, risk/benefit profile, study design, objectives and endpoints. The application should also include sections describing the technical details of the study design and what aspects of the design the Sponsor proposes to be used for disclosure. The sponsor may also provide preferred dates for the first statistical review meeting.
FDA response to the pilot application	Assuming content of disclosure material is not an issue – 30 days; otherwise 45 days. If the FDA wants to discuss/negotiate the disclosure material, FDA could notify the sponsor 15 days after receiving Sponsor's request to join the pilot.
First statistical review – meeting timelines	In general, 30–45 days after the acceptance into the pilot: Before the Type B (EoP) meeting (*e.g.,* for pilot requests submitted prior to a request for a Type B (EoP) meeting) After the Type B (EoP) meeting (*e.g.,* for pilot requests submitted after the PMP package submission).
First statistical review - materials/documents	Presentation describing the complex simulations and/or statistical methodology, shared with the FDA 2 business days before the meeting. Simulation programs with all relevant documentation and/or documentation/publications referenced at the meeting, shared with the FDA within 1 week following the meeting.
Communication between the statistical review meetings	At least one formal letter from the FDA to the Sponsor including comments/questions related to the study design and/or simulation outcomes, 30 days before the second statistical review meeting (if the timing between the meetings is 120 days) and 15 days or less (if the timing was negotiated to be shorter). During the time between the two meetings, the Sponsor should have a designated person addressing the FDA questions related to the simulation programs, external data sources (if proposed to be utilized) and/or any other technical issues related to the study design.

Second statistical review – meeting timelines	The goal should be to hold the meeting 120 days following the first statistical review meeting. The FDA and the Sponsor may agree to hold the meeting 30-90 days after the first statistical meeting.
Second statistical review - materials/documents	Presentation addressing FDA comments/concerns shared with the FDA 2 business days before the statistical review meeting. To avoid duplicative communication, formal revisions to the study design should be included in the Sponsor's response following the Type B (EoP) meeting.

II. Recommendations on communications regarding acceptance or rejection of proposals

BIO believes there could be considerable interest in the ICTD Pilot Program, leading to potentially significant time and resources required on the part of industry to develop and of FDA to review and respond to proposals for acceptance.

BIO recommends that FDA develop an "ICTD Pilot Application FDA Review Form" ("Review Form") to help the review process. Using standardized Application and Review forms and making the blank templates public could reduce the risk of a Sponsor misinterpreting an application response. Although not an expansive list, the risk of misinterpretation could include the following two scenarios: (1) over-interpreting acceptance into the pilot as FDA's endorsement of the proposed approach, or (2) misinterpreting a rejection of a pilot proposal as FDA's definitive view that the design is not acceptable for use in the development program.

BIO recommends that the Review Form be a single form letter that applicants receive in response to a pilot program submission, which consists of standard common data elements while retaining the flexibility of open fields to provide context for FDA action. These standard data elements should be created in a manner that makes them amenable for internal and external tracking and generation of performance metrics (i.e., number of submissions received, granted, etc.) to help assess the value and resource expenditure.

Regarding the standard form, it is suggested the Agency consider using relevant aspects of the Checklists for Acceptance and Filing of PMAs from the CDRH Guidance titled "Acceptance and Filing Reviews for Premarket Approval Applications (PMAs)." For example, the ICTD pilot program Review Form to an Application Form should contain the following standard information/data elements:

- Acceptance into the pilot
- Refusal to accept into the pilot:
  - With the possibility to revise the proposal
  - Without the possibility to revise the proposal
- Statement of FDA's goals for the pilot program

- Emphasis of educational goal of the pilot program to promote acceptability of innovative clinical trial design within FDA and broader utilization by industry to facilitate bringing safe and effective products to patients
- FDA recommendations/advice on the use of other regulatory tools to get feedback and agreement on the design (*e.g.,* discussions with the review division, Special Protocol Assessment)
- Clear dates for approval and acceptance into the pilot in order to keep track of timelines and deadlines (*e.g.,* the two additional meetings included in the pilot)
- Options (resources permitting) for sponsors to get additional feedback from FDA about the decision
- Rationale for FDA recommendation action. This data element could include the following general statements:
    - The design submitted is of interest to the FDA and potentially acceptable following discussions with the review division;
    - The proposal is not amenable to public learning because a similar design was accepted into the pilot;
    - The design submitted provides limited information for public learning in the near-term; or
    - Insufficient information about the design was provided by the Sponsor to permit evaluation by FDA as a pilot candidate.

To clarify the rationale for FDA's recommendation action, regardless of FDA's decision, the form letter should have a section that adequately and substantially addresses the rationale for the action. This is particularly important in instances in which proposals are rejected, since these scenarios present the greatest risk of misinterpretation of the suitability of ICTDs. Although it is difficult to predict the volume of proposals FDA will receive, and recognizing there may be differences by division/Center, we recommend that FDA communicate the decision to all ICTD applicants who submit proposals.

III. Recommendations on disclosure of information

Participation in the pilot program, including agreement on information disclosure, is voluntary and at the discretion of the sponsor.[1] Since the pilot proposals will include ongoing development programs, sponsors would already provide FDA with non-disclosable, detailed trial information, interim or final data among other information, through usual meetings, submissions, and communications as part of their development programs. FDA public disclosures of studies submitted to this pilot as "case studies" (*e.g.,* in guidance or public workshop) should focus on information most beneficial to furthering FDA and industry's joint goals of advancing the use of innovative clinical trial designs and enabling their broader acceptance by the FDA to support therapeutic product development, while not compromising a sponsor's sensitive or confidential information (*e.g.*, Confidential Commercial Information, or "CCI"). This will require a clear and non-burdensome process for a sponsor and FDA to agree on what may or may not be disclosed to the public.

Because innovative clinical trial designs are highly variable in approach and statistical design, sponsor consent to FDA disclosure of piloted study information would logically be on

[1] *PDUFA Reauthorization Performance Goals and Procedures, Fiscal Years 2018 – 2022,* p. 32.

a proposal-by-proposal basis. In order to help provide some standardization to information proposed by the sponsor for disclosure, FDA may wish to consider a specific section in sponsor pilot applications dedicated to "Disclosures." In this section, the sponsor could propose information consented for public disclosure by the FDA, should the proposal be accepted into the pilot program. The length of this section could be comparable to the Abstract of a manuscript.

"Disclosures" should be limited to the information necessary to inform and teach aspects of the use of the proposed innovative design or statistical methodology, while not disclosing, or by anonymizing, other information. For instance, disclosing parameters like: indication being sought, mechanism of action, molecular structure, the sponsor, study groups, schedule of interventions, sample analyses to be performed, study agents, recruitment strategies, adverse events, subject-level data, etc., are presumed unnecessary to achieve the pilot goals. If disclosed, endpoints could be described generally (*e.g.,* "reduction in a key biomarker value to a medically significant effect size"). Statistical and trial design disclosures could include: sample size and power determination, null and alternative hypothesis, an overview of key operating characteristics, as well as assumed rates for dichotomous outcomes or mean and variance for continuous outcomes. Further disclosures might include parameters material to the proposed innovative approach such as simulation objectives, scenarios of truth, operation assumption (*e.g.,* drop-out rate, enrollment rate, etc.), modeling characteristics, critical study design characteristics including any adaptive elements if the innovative design is adaptive (*e.g.,* decision criteria to add/drop a dose, etc.); and, if Bayesian, how the Bayesian approach is being used for design and/or analysis purposes. FDA may wish to negotiate with a sponsor regarding information the agency would like to disclose for a sponsor's pilot application; however, the particular disclosures would be specified by the sponsor.

Appendix B

Promoting the Use of Complex Innovative Designs in Clinical Trials – Case Studies

Public Meeting

March 20th, 2018

Docket No. FDA-2018-N-0049

Bio Biotechnology Industry Organization

Case Studies

- High-level examples of innovative clinical trial designs
  - Recommended by industry to be considered in the pilot program
  - Historically low level of regulatory acceptance

Expectations for Case Study Discussion

- There might be a wide range of designs sponsors may submit to the CID pilot
  - From conventional to very innovative

- The purpose is to provide insight into the types of CID that industry would like to see in the pilot program and to share our perspective on the value of these CID

Expectations for Case Study Discussion *(cont.)*

- We hope to get insights from FDA on:
  - What adequate protocol documentation might contain (i.e., tangible examples associated with Section IX.B in the *Adaptive Design Clinical Trials for Drugs and Biologics Draft Guidance*)
  - The role of prospective statistical analysis plan (e.g., similar to Section VII.E in the *Adaptive Design Clinical Trials for Drugs and Biologics Draft Guidance*)

Case Study 1 – Open label study

- **Description of the clinical trial**
  - Type of CID: Open-label study with external control for small population, including, but not limited to, genotype of common diseases (e.g., cardiovascular disorders) or rare conditions
  - Goals: To conclude the efficacy of a molecule based on:
    - Comparison with external control from a natural history study or from placebo or active control in external clinical trials matched by key enrollment criteria or by propensity score or other mechanisms of matching
- **Value proposition for use of the CID**
  - Efficiently use available data
  - Maximizing information from treated patients and avoid unethically treating/wasting patients with placebo

Case Study 2 – Bayesian

- **Description of the clinical trial**
  - Type of CID: Bayesian augmented control design with a small placebo or active control for
    - Pediatrics investigation plans for both rare and common diseases (e.g., rheumatologic conditions, asthma)
    - Small population
  - Goals: To conclude the efficacy of a molecule by borrowing historical information based on covariate-adjusted Bayesian hierarchical model, power prior or commensurate power prior method
- **Value proposition for use of the CID**
  - Reducing sample size without lowering the power of the study
  - Concurrent placebo control allows robust assessment of efficacy through proper determination of statistical assumptions

Case Study 3 – Adaptive Trial

- **Description of the clinical trial**
  - Type of CID: Adaptive trial to evaluate a combination of two unapproved products to treat or prevent disease with serious complications (e.g., CDI recurrence)
    - Each component (A,B) acts on the same primary endpoint
    - Limited phase 2 data on A or B used alone; results suggest combination (A+B) is effective
  - Goals: Provide efficient method to select optimal regimen/evaluate contribution of individual components/demonstrate efficacy
  - Design: 4 arm factorial (A, B, A+B, placebo)
    - Interim analysis allows one or both individual components to be dropped
    - Multiplicity considerations: how to control type 1 error across and within sets of comparisons (A+B vs. A,B and A+B,A,B vs. Placebo) and across interim and final analyses – have major impact on operating characteristics
- **Value proposition for use of the CID**
  - Limits number of patients assigned to sub-optimal or ineffective therapy
  - More efficient use of patients and trial resources following interim analysis

Case Study 3 *(cont.)*

- **Value proposition for use of the CID *(cont.)***
  - Strategy for allocation of type 1 error can improve feasibility of dropping arm(s) at interim analysis
    - Propose not requiring strong control across the two sets of comparisons and use simulations to determine overall type 1 error
    - Evaluate different allocations between interim and final analyses using simulations to determine operating characteristics and select final design
  - Consider alternate decision rules for selecting components at final analysis
    - Specify that (A+B) vs. placebo is the primary comparison; assume efficacy is clearly demonstrated
    - Propose retaining component if it contributes, e.g., at least 35% of the total effect of the combination
    - Require adequate power to differentiate individual component from placebo if it contributes, e.g., at least 80% of total effect
    - Use simulations to determine operating characteristics of decision rule

Case Study 4 – Platform Trial

- **Description of the clinical trial**
  - Type of CID: Studies which are designed to assess multiple interventions in the context of a single disease in a perpetual manner, with interventions entering or leaving the study on the basis of pre-defined rules. These designs are often referred to as platform trials (Woodcock and LaVange (2017)).
  - Examples:
    - A study to evaluate multiple therapies for Ebola virus (PREVAIL II).
    - Evaluation of multiple therapies in Lung Cancer within multiple biomarker-defined subgroups (LUNG-MAP)
  - Goals: To demonstrate efficacy/safety of an intervention

Case Study 4 *(cont.)*

- **Value proposition for use of the CID**
  - Efficiency of assessing multiple interventions in one study
    - Use of common control data to evaluate efficacy of multiple therapies
    - Reduce number of patients exposed to control interventions
    - Allow interventions to enter the study at differing times
  - Ability to focus on interventions that demonstrate promising efficacy/safety, while “dropping” those that don’t
  - Explore and assess common principles to guide the innovative statistical approaches to study design and analysis including but not limited to:
    - Adaptive design aspects of trial design, response-adaptive randomization;
    - Statistical frame work (e.g., Bayesian approaches) with focus on demonstration of efficacy in context of pivotal trial;
    - Extent of control data usable for interventions entering later into study (i.e., assessing temporal changes in control data, down-weighting control data from earlier in study)
    - In the context of a perpetual trial: (1) what control data can be used for comparisons against a novel intervention and (2) if and when can the control be changed (i.e., one of the new interventions demonstrates efficacy and becomes the control)

Case Study 5 – Basket Design

- **Description of the clinical trial**
  - Type of CID: Basket studies which are designed to answer questions about a specific intervention (agent +/- SOC) in multiple diseases or disease subtypes and/or multiple patient populations where there is some commonality among the diseases, subtypes or populations. These designs are commonly referred to as Basket designs (Woodcock and LaVange (2017))
  - Examples:
    - To test an intervention across different cancers with shared molecule etiology
    - To test an intervention across different infectious diseases driven by same pathogen
    - To test an intervention in a disease across different patient populations (e.g., patients with varying stage of disease where SOC differs, subgroups of age etc.)
    - To test an intervention across rare diseases where a single study may be infeasible
- Goals: To demonstrate efficacy/safety of intervention within and/or across diseases/subtypes/populations

Case Study 5 *(cont.)*

- **Value proposition for use of the CID**
  - Maximize efficient use of study information and magnify the significance of individual test based on exchangeability of treatment effect and validate the adequacy of different significance levels, composite vs. individual
  - Ability to focus on promising diseases or patient populations and evaluate new therapies in the context of “precision medicine”
  - To consider generalization to a trial with different primary endpoints across the baskets
  - Explore and assess common principles to guide the innovative statistical approaches to study design and analysis including but not limited to
    - (1) adaptive design aspects of trial design (e.g., dropping/adding baskets);
    - (2) statistical frame work (e.g., Bayesian approaches, independent tests vs. methods for sharing/pooling data across buckets)
    - (3) considerations for study designs (e.g., minimum sample size per bucket (major benefit for rare disease studies), ability to extrapolate to buckets not studied or not powered (e.g., approve for all cancers with X-mutation))