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The U.S. Food and Drug Administration's Complex Innovative Trial Design Pilot Meeting Program: Progress to date

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Abstract

Background: The Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research of the U.S. Food and Drug Administration have been leaders in advancing science to protect and promote public health by ensuring that safe and effective drugs and biological products are available to those who need them. Recently, new therapeutic discoveries, increased understanding of disease mechanisms, the need for innovation to optimally use resources, and global public health crises have led to an evolving drug development landscape. As a result, the U.S. Food and Drug Administration and medical product developers are faced with unique challenges and opportunities. The U.S. Food and Drug Administration is proactively meeting the challenges of this evolving landscape through various efforts, including the Complex Innovative Trial Design Pilot Meeting Program. Our focus, here, will be on the pilot meeting program.

Methods: The U.S. Food and Drug Administration has defined a process to facilitate the implementation of the Complex Innovative Trial Design Pilot Meeting Program. The process is transparent and outlines the steps and timeline for submission, review, and meetings.

Results: Five submitted meeting requests have been selected for participation in the Complex Innovative Trial Design Pilot Meeting Program.

Conclusion: The pilot meeting program has been successful in further educating stakeholders on the potential uses of complex innovative designs in trials intended to provide substantial evidence of effectiveness. The selected submissions, thus far, have all utilized a Bayesian framework. The reasons for the use of Bayesian approaches may be due to the flexibility provided, the ability to incorporate multiple sources of evidence, and a desire to better understand the U.S. Food and Drug Administration perspective on such approaches. We are confident the pilot meeting program will have continued success and impact the collective goal of bringing safe and effective medical products to patients.

Keywords

Food and Drug Administration, complex innovative trial designs, pilot program

Background

In the letter describing the goals of the sixth iteration of the Prescription Drug User Fee Amendments,[1] complex innovative designs are referred to as "complex adaptive, Bayesian, and other novel clinical trial designs," including those requiring simulations to estimate the operating characteristics. However, there is no fixed definition of complex innovative trial designs. The meaning of what is considered an innovative design can change over time and can be specific to the therapeutic indication. We consider complex innovative trial designs to be those designs that have rarely or never been used to provide substantial evidence of effectiveness in new drug applications or biologics license applications. Some examples of complex innovative trial design features include novel use of external or historical control data, formal incorporation of prior knowledge into the design, and adaptations to multiple design aspects based on accumulating data.[2]

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An overarching goal of using complex innovative trial designs is to improve clinical trial efficiency with scientific methods that can reliably answer the questions of interest and facilitate regulatory decisions. Clinical trial efficiency may translate into a reduction in numbers of patients needed for a trial, accelerated product development, or optimized product development (e.g. maximum information obtained from the research effort). Complex innovative trial designs may be especially promising when conventional approaches may not be feasible or optimal, such as in areas where the population size is small or limited or where there is an unmet medical need.[3] Specifically, for small populations, design innovations that can reduce sample size may not only speed development but also make infeasible development programs feasible. In the setting of an unmet medical need where a conventional trial may not be feasible or optimal, a complex innovative design may result in accelerated product development and earlier product availability to patients.

The use of complex innovative trial designs to provide the substantial evidence of effectiveness required for the U.S. Food and Drug Administration (FDA) to approve a drug or biological product has been limited across a broad range of therapeutic areas. This is evidenced by the lack of publications describing clinical development programs utilizing novel designs that ultimately resulted in the approval of drug or biological products. In a public workshop convened by the FDA, it was posited that a barrier to the use of complex innovative trial designs within submissions to the FDA was a lack of clarity around regulatory acceptance of such designs.[4] Moreover, FDA is generally unable to publicly discuss novel design proposals while an application is pending or if the product is not ultimately approved. The pilot meeting program provides a framework and infrastructure for the development and implementation of innovative designs across therapeutic areas. The pilot meeting program also includes a disclosure element that permits FDA to discuss aspects of the designs accepted into the pilot program to promote increased clarity, consistency, and transparency. The disclosure feature of the pilot program permits stakeholders to learn from the designs accepted into the program and broadens knowledge of the appropriate use of complex innovative trial designs for the purpose of regulatory submissions.

FDA announced the Complex Innovative Trial Design Pilot Meeting Program in the *Federal Register* on 30 August 2018.[5] A website was also launched to serve as a resource for stakeholders.[6] Created to facilitate the use of innovative clinical trial designs across therapeutic areas, the pilot meeting program is intended especially for designs which require simulations to estimate the operating characteristics of the trial. The duration of the pilot program is 5 years. The program provides participants the opportunity for increased engagement with regulatory staff on the proposed designs through two meetings with the Agency. These meetings occur within a span of approximately 120 days. Based on the analytical complexities of the designs and need for simulations, the meetings are led by statisticians. However, clinicians, pharmacometricians, and relevant disciplines participate in the meetings and are germane to the discussions. FDA grants up to two meeting requests per quarter, prioritizing selections based on the therapeutic need of the product under evaluation and innovative features of the design. Designs accepted into the pilot program serve as educational examples to facilitate the science and use of complex innovative trial designs. Subject to a disclosure agreement between FDA and pilot program participants, the Agency may publicly present elements of the design and analysis as case studies even when the medical product studied in the trial has not yet been approved.

Methods

FDA accepts meeting requests on a rolling basis each quarter, with the deadline for submission at the end of each quarter (31 March, 30 June, 30 September, and 31 December). After the quarter ends, FDA evaluates each request based the criteria outlined on the Complex Innovative Trial Design webpage.

For those submissions deemed eligible, FDA evaluates the meeting requests and selects those to proceed to disclosure discussions. If FDA reaches an agreement with the sponsors on information about their designs that can be publicly disclosed, FDA will grant their meeting requests. The elements FDA intends to publicly disclose as part of the pilot program are available on the website. The process described above, including the approximate timing of each step, is shown in Figure 1.

Results

At the time of writing, FDA had selected five submitted meeting requests. The selected meeting requests consisted of drug products in neurology, analgesia, rheumatology, and oncology. Denied meeting requests were due to a lack of clarity on an appropriate primary endpoint in a specified therapeutic area, determination that a submission did not involve an innovative design but rather a revised primary endpoint in an ongoing trial, and a finding that a proposal had already received extensive advice by the relevant review division. Sponsors of denied requests were encouraged to seek Agency feedback through existing channels. For the current publication, we provide a brief overview of the selected submissions. These overviews primarily reflect the initial proposal and do not represent modifications based on iterative dialogue.

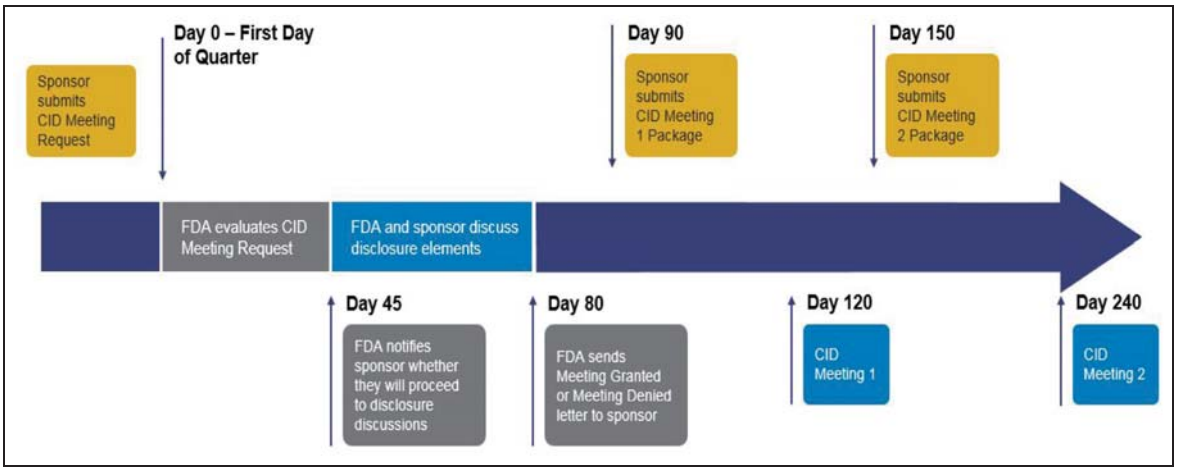

Figure 1. Pilot program process.
CID: Complex Innovative Trial Design.

Overview of the first meeting request

The first proposal FDA accepted into the pilot program outlined a randomized, double-blind, placebo-controlled study of a low- and high-dose investigational treatment in ambulatory patients with Duchenne Muscular Dystrophy, a rare disease.

The original proposal consisted of a two-stage design with patients randomized to placebo or a low dose in Stage 1. Following a review of available safety data and data from ongoing studies, the sponsor would commence Stage 2 with inclusion of a high dose, if deemed appropriate. Additional patients would be randomized in Stage 2 to receive placebo, low dose, or high dose in a ratio designed to ensure a specified number of patients per arm (inclusive of Stages 1 and 2).

The treatment effect of the investigational product would be evaluated through the primary endpoint that measures the change from baseline in dystrophin level through a specified timepoint and an important secondary endpoint that measures the change from baseline in a clinical outcome assessment. The sponsor would analyze both endpoints via a Bayesian repeated measures model utilizing multiple interim analyses to determine study adaptations. Potential adaptations included stopping the trial for efficacy or lack of safety, sample size modification, dropping of a treatment arm, pooling of doses, and changes to the randomization ratio. The sponsor would also explore augmentation of the placebo arm with historical control data. Simulations were to be conducted to investigate the impact of the possible adaptations and the placebo augmentation strategy on the operating characteristics.

Based on the meeting request and the initial meeting package, FDA provided preliminary comments that included the need for additional clarity regarding the interim analyses, placebo augmentation, and specified analysis models. FDA also provided several recommendations for simulation scenarios, noting that the simulations should incorporate all the adaptations, include evaluation of the performance of estimates of treatment effects, and cover the full range of plausible values for all the nuisance parameters.

Overview of the second meeting request

The second proposal FDA accepted into the pilot program pertains to a randomized, double-blind, group sequential, non-inferiority study comparing an investigational drug to an active control in a pediatric multiple sclerosis population.

The sponsor proposed a primary endpoint assessing relapse rate. Non-inferiority of the investigational treatment to the active control would be evaluated using a Bayesian negative binomial model. The proposed non-inferiority margin was based on a completed trial in the population of interest. Moreover, the proposal included a Bayesian framework to incorporate information from available studies as prior distributions for the parameters of the statistical model. Specifically, the sponsor proposed meta-analytic predictive priors that borrow strength across different studies through hierarchical models. The prior would be further explored by specifying the prior as a mixture of informative and non-informative prior distributions. The sponsor also proposed an interim analysis for efficacy.

Initial discussions focused on the appropriateness of the non-inferiority margin. In addition, FDA requested the following: additional information on the selected external studies since the comprehensiveness of the information was not clear; an exploration of the impact

of using the same data to both inform the margin and to leverage external information; and additional simulations varying nuisance parameters and priors.

Overview of the third meeting request

The third proposal FDA selected includes a master protocol to evaluate multiple interventions across multiple chronic pain conditions. The sponsor proposed a multicenter, randomized, double-blind, placebo-controlled master protocol. The sponsor intends to include multiple pain conditions and interventions. The primary measure of interest would be pain relief assessed via the mean change from baseline in a numeric rating scale. Each intervention would be compared to a placebo group. The primary endpoint would be evaluated using a Bayesian mixed-model repeated measures analysis that would allow for borrowing patient information from the placebo groups within a pain condition and borrowing information on the treatment difference across different pain conditions for the same active intervention. The sponsor proposed hierarchical modeling to allow for flexibility in the amount of borrowing. In addition, data from external sources could be used to develop informative priors on some model parameters.

Initial discussions between FDA and the sponsor pertained to the potential for drift in the placebo response, the assumption of exchangeability among patients with different pain conditions, and the impact of missing data frequently encountered in chronic pain trials.

Overview of the fourth meeting request

The fourth selected proposal outlined a Bayesian adaptive trial to evaluate multiple doses of an investigational product in systemic lupus erythematosus. Eligible patients would be randomized to placebo, low dose, medium dose, or high dose. The primary outcome would be a responder index at a specified timepoint. The primary analysis would utilize a Bayesian hierarchical model with dynamic borrowing to estimate response rates across treatment groups. Proposed features of the trial included response adaptive randomization and multiple adaptive interim analyses. FDA feedback focused on the need for comprehensive simulations that consider ranges of nuisance parameter values and additional scenarios to evaluate the operating characteristics of the design.

Overview of the fifth meeting request

The fifth proposal included a multicenter, randomized, controlled trial to evaluate an investigational treatment added to an existing combination regimen compared to the existing regimen alone in an oncology setting with an unmet need. The trial would include both an internal control arm as well as an external control arm. The primary outcome would be progression free survival, and the primary analysis would utilize the internal control data. Analyses of key secondary outcomes such as overall survival would additionally incorporate external, concurrent controls using a Bayesian dynamic borrowing approach. FDA feedback focused on the patient population, assumptions of the proposed model, and the use of a propensity score as a covariate in the model.

Conclusion

FDA will periodically review the Complex Innovative Trial Design Pilot Meeting Program to identify lessons learned and necessary program adjustments. Our experience to date indicates that there is a need for additional FDA clarity around expectations for the simulation plan and simulation report. Moreover, the pilot program has highlighted the iterative nature of innovative designs and the importance of multidisciplinary dialogue around the designs.

Thus far, the selected submissions have all utilized a Bayesian framework. This is not surprising as Bayesian approaches may be well-suited for some complex innovative designs because they can provide flexibility in the design and analysis of a trial. In addition, Bayesian inference may be appropriate in settings where multiple sources of evidence are considered, such as has been proposed in some of the selected submissions.[2] The number of Bayesian proposals may also be the result of stakeholders' desire to better understand the acceptance of Bayesian methods within the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research. The methodology used in complex innovative designs may be based on either existing methodology or methodology bespoke to the trial. Moreover, the methodology may be innovative within the context of the product class, indication, or regulatory submission. A proposal that may be appropriate for one product class or indication may not be appropriate for another.

Finally, the goal of the Complex Innovative Trial Design Pilot Meeting Program is to encourage the use of value-added complex innovative trial designs to facilitate informed regulatory decision-making. We believe the program will achieve this goal through the iterative meeting process and increased education from the case examples. We are confident that through innovation and collaboration, the program will succeed and achieve its ultimate goal of bringing safe and effective medical products to patients.

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