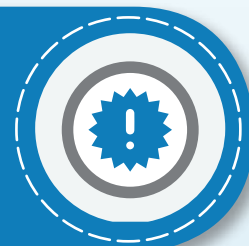


Interacting with the FDA on Complex Innovative Trial Designs for Drugs and Biological Products

Guidance for Industry

What is recommended in this guidance?

This guidance provides recommendations to sponsors and applicants on interacting with the FDA on complex innovative trial design (CID) proposals for drugs or biological products and describes the type of information FDA recommends submitting.



CID Definition

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. There is no fixed definition of CID because what is considered innovative or novel can change over time.



Roadmap for interacting with sponsors on CID Proposals



MEETING WITH FDA

Sponsors should seek early interaction with FDA. In general, sponsors should use existing interaction pathways, 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. An additional option for interaction is through the CID Pilot Meeting Program.



SUBMISSION DOCUMENTATION

The specific documentation needed will depend on the type of proposal submitted, but in general, 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.



BAYESIAN CID PROPOSALS

If a sponsor chooses to submit a Bayesian CID proposal, the sponsor should include appropriate documentation for review, including descriptions and rationales for two key items:

1. prior distributions*
2. study decision criteria for primary and key secondary endpoints.



SIMULATIONS

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. If a CID proposal includes simulations, structuring part of the End of Phase 2 discussions around Phase 3 trial simulation plans can help FDA reviewers and the sponsor consider the scenarios to be explored in simulations and the underlying trial assumptions, such as accrual rate or likely control group outcomes.

*The Bayesian method relies on accurate specification of the prior probability distribution of unknown parameters to control the chance of erroneous conclusions. 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 down weighting of earlier data relative to contemporaneous data or initial skepticism regarding the likelihood of large treatment effects.

Guidance Snapshots are a communication tool and are not a substitute for the guidance document.

To learn more about interacting with sponsors on complex innovative trial designs for drugs and biological products, read the [guidance](#)



Background About the Guidance

CIDs have the potential to improve trial efficiency, for example making trials smaller and faster. However, with these potential advantages come additional challenges, due in part to limited experience with these trial designs in regulatory decision-making. Due to their complexity and in some cases to their novelty, CID designs often call for additional regulatory review documentation. FDA is issuing this guidance to help ensure successful interactions between sponsors and the FDA that support the regulatory review of CID proposals for trials intended to provide substantial evidence of effectiveness for drugs and biologics.

Drug Development Timeline – When to Apply the Guidance Recommendations?



During Clinical Development:

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.

Guidance Recap Podcast – Hear Highlights Straight From FDA Staff

Speaker: Dr. Greg Levin, Deputy Director of the Division of Biometrics III in the Center for Drug Evaluation and Research’s Office of Biostatistics



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