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Advancing the Use of Complex Innovative Designs in Clinical Trials: From Pilot to Practice

Public Workshop

March 5, 2024

Welcome and Opening Remarks

John Scott, PhD
Director, Division of Biostatistics
Office of Biostatistics and Pharmacovigilance
Center for Biologics Evaluation and Research
U.S. Food and Drug Administration

Background

- Clinical trials form the backbone of evidence of safety and effectiveness needed for drug and biologic approval
- Costs and complexity of trials have ballooned in recent decades
- There is need for innovative approaches to answer complex questions and to improve trial efficiency
  - Adaptive designs
  - Bayesian approaches
  - Incorporating external data
- Result: FDA's Complex Innovative Trial Design (CID) review program

PDUFA VI

Objective: To facilitate the advancement and use of complex innovative designs

- Develop staff capacity
- Conduct a pilot program
- Convene a public workshop
- Publish draft guidance
- Develop or revise relevant MAPPs, SOPPs, and/or review templates

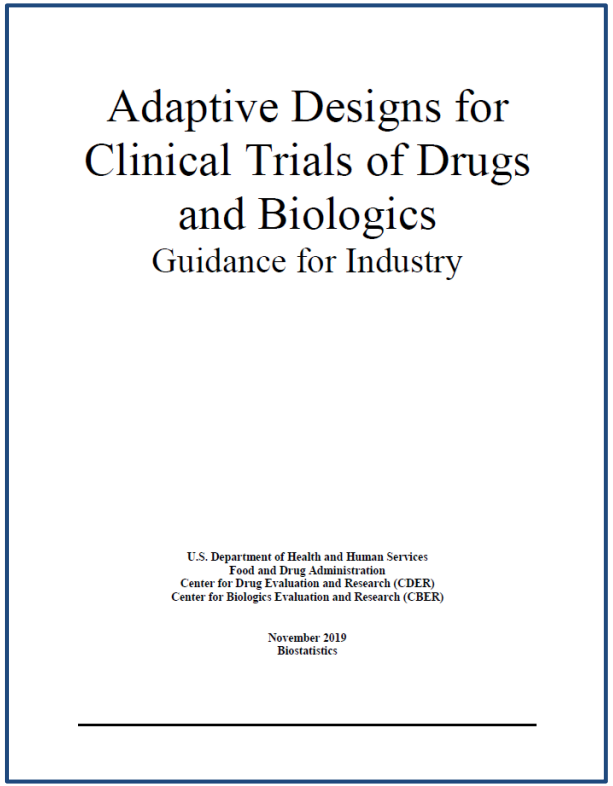
Pilot CID Meeting Program

- Joint effort between FDA's Center for Drugs (CDER) and Center for Biologics Evaluation and Research (CBER)
- Sponsors:
  - Submit designs
  - Have the opportunity to engage with regulatory team on designs via two additional meetings
- FDA:
  - Selects up to 2 submissions per quarter
  - Uses the designs as case studies for outreach and education
- Meetings led by Biostatistics groups (CDER/OTS/OB or CBER/OBPV/DB) with participation from all relevant disciplines
- Duration: From 2017 - 2022

CID Program Case Studies

- 6 accepted submissions span several therapeutic areas
  - Neurology
  - Analgesia
  - Rheumatology
  - Oncology
  - Includes adult and pediatric rare diseases
- Designs incorporated
  - Bayesian hierarchical modeling
  - Use of informative priors
  - Master protocol

CID Guidances

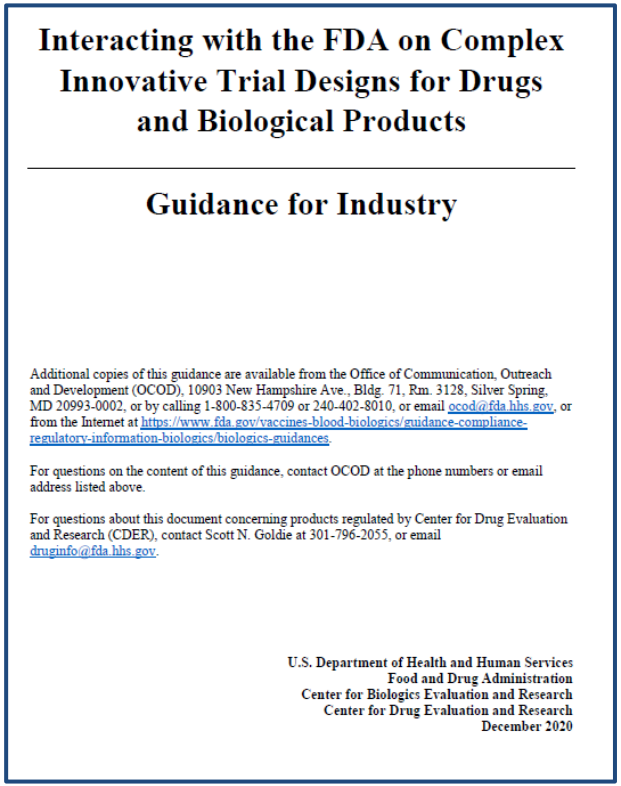


Adaptive Designs for Clinical Trials of Drugs and Biologics

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

November 2019
Biostatistics



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

Guidance for Industry

Additional copies of this guidance are available from the Office of Communication, Outreach and Development (OCOD), 10903 New Hampshire Ave., Bldg. 71, Rm. 3128, Silver Spring, MD 20993-0002, or by calling 1-800-835-4709 or 240-402-8010, or email ocod@fda.hhs.gov, or from the Internet at https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances.

For questions on the content of this guidance, contact OCOD at the phone numbers or email address listed above.

For questions about this document concerning products regulated by Center for Drug Evaluation and Research (CDER), contact Scott N. Goldie at 301-796-2055, or email druginfo@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
Center for Drug Evaluation and Research
December 2020

Now: PDUFA VII (2022 – 2027)

Objective: To facilitate the advancement and use of complex adaptive, Bayesian, and other novel clinical trial designs

- Continue to develop staff capacity
- Continue the paired meeting program
- **Convene a public workshop**
- Publish draft Bayesian guidance

Today's Workshop

- To discuss aspects of complex adaptive, Bayesian, and other novel clinical trial designs
  - Considerations for external data sources
  - Bayesian statistical methods
  - Simulations
  - Clinical trial implementation
- Three case studies
- Panel discussion

Speakers* and panelists

Panelist	Affiliation
Frank Bretz, PhD	Novartis
Dean Follman, PhD	NIAID / NIH
Frank E Harrell, PhD	Vanderbilt University & FDA
Rebecca Hubbard, PhD	University of Pennsylvania
J. Jack Lee, MD, MD, DDS	University of Texas MD Anderson Cancer Center
Stephen Ruberg, PhD	Analytix Thinking
*Roger J. Lewis, MD, PhD	UCLA & Berry Consultants
*Herbert (Herb) Pang, PhD	Genentech / Roche
*Karen Lynn Price, PhD	Eli Lilly and Company

Thanks

- Tuan Pham, CDER CID project coordinator
- CDR Christopher Egelebo, CBER CID project coordinator
- CID Steering Committee
- CID Selection Committee
- CID Education Subcommittee
- CBER and CDER review staff
- White Oak AV team

Special Thanks

Dionne L. Price, PhD
1971 - 2024

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The Chilled Platelet Study (CHIPS): An Adaptive, Storage Duration Finding Trial

Roger J. Lewis, MD, PhD

Advancing Innovation: A Master Protocol for Patients with Chronic Pain

Karen Lynn Price, PhD

Break

Will return at 10:50am ET

A Case Study of a Hybrid Control Design in Diffuse B-Cell Lymphoma

Herbert (Herb) Pang, PhD

Lunch Break

Will return at 12:30pm ET

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Panel Discussion

Panelists

Panelist	Affiliation
Frank Bretz, PhD	Novartis
Dean Follman, PhD	NIAID / NIH
Frank E Harrell, PhD	Vanderbilt University & FDA
Rebecca Hubbard, PhD	University of Pennsylvania
J. Jack Lee, MD, MD, DDS	University of Texas MD Anderson Cancer Center
Stephen Ruberg, PhD	Analytix Thinking
Roger J. Lewis, MD, PhD	UCLA & Berry Consultants
Herbert (Herb) Pang, PhD	Genentech / Roche
Karen Lynn Price, PhD	Eli Lilly and Company

Discussion question 1

Each of the case studies this morning used a Bayesian statistical framework. Did they need to be Bayesian, or could similar study designs have been implemented using frequentist approaches? What advantages, if any, did Bayesian methods provide in these examples?

Discussion question 2

For late-stage studies with a frequentist design, the maximum Type I error rate is typically controlled at .025 (one-sided). Is there a direct analogue for Bayesian designs? What are the specific design characteristics that you see as most critical to support regulatory decision-making for Bayesian trials, especially trials that use informative priors to incorporate external data in the study analyses?

Discussion question 3

Regarding the use of external data in trials, how should external data sources be chosen? How would you advise FDA to evaluate a proposed external data source? What are some approaches to identifying and mitigating bias in the use of external data?

Discussion question 4

Consider a Phase 3 trial conducted after a very similarly-designed Phase 3 (or Phase 2) trial of the same treatment in the same population. What are the advantages or disadvantages of analyzing the trials independently vs. borrowing information vs. meta-analysis?

Discussion question 5

How should exchangeability be assessed in late-stage trials that borrow external information? Are some methodologies more robust than others to violations of exchangeability? What should be done in cases where there is strong evidence of heterogeneity between prior data sources and trial data?

Discussion question 6

How should prior parameters that govern the amount of borrowing be chosen when designing a trial? Should the amount of borrowing be quantified and, if so, how? How would you advise regulators to use the amount of borrowing to make decisions about the appropriateness of a proposed study design?

Discussion question 7

Under what circumstances can clinical trial simulations provide enough confidence in trial operating characteristics to support a confirmatory trial design proposal?

Discussion question 8

How do we ensure CIDs are fit for purpose and not complexity for its own sake? Are there advantages to sequential trials without additional adaptations?

Discussion question 9

Do you have any suggestions for ways FDA can support the appropriate use of complex designs in addition to the CID Paired Meeting Program?

Break

Will return at 2:45pm ET

Question and Answer Session

Closing Remarks

John Scott, PhD
Director, Division of Biostatistics
Office of Biostatistics and Pharmacovigilance
Center for Biologics Evaluation and Research
U.S. Food and Drug Administration

Summary

- Three case studies:
  - CHIPS
  - Chronic pain master protocol
  - Hybrid control in diffuse B-cell lymphoma
- Robust panel discussion covering
  - External data sources
  - Bayesian methodologies
  - Trial simulations

Thanks: Panelists and Public Participants

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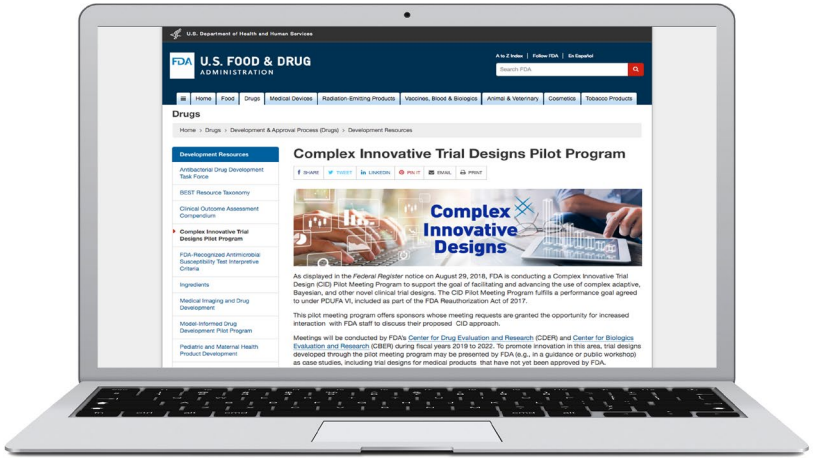
Next steps

- The docket for public comments for this workshop is open until April 4, 2024
- FDA will review and digest the feedback we've received today and from comments to the docket
- Commitment to publish draft Guidance on the Use of Bayesian Methodology in Clinical Trials of Drugs and Biologics by September 30, 2025
- A transcript and link to video of today's workshop will be posted on the event website and FDA's CID website when available

More information



[FDA Complex Innovative Trial Design Pilot Program Home Page]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