Statistical Updates from the United States Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER)

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EFSPI Regulatory Statistics Workshop
September 12, 2024

Outline

- Introduction
- Brief updates on several statistical topics
  - Covariate adjustment
  - Real-world evidence
  - Master protocols
  - Artificial intelligence and machine learning
  - Diversity in clinical trials
  - Adaptive designs and complex innovative designs (CIDs)
- Other topics of interest

Introduction

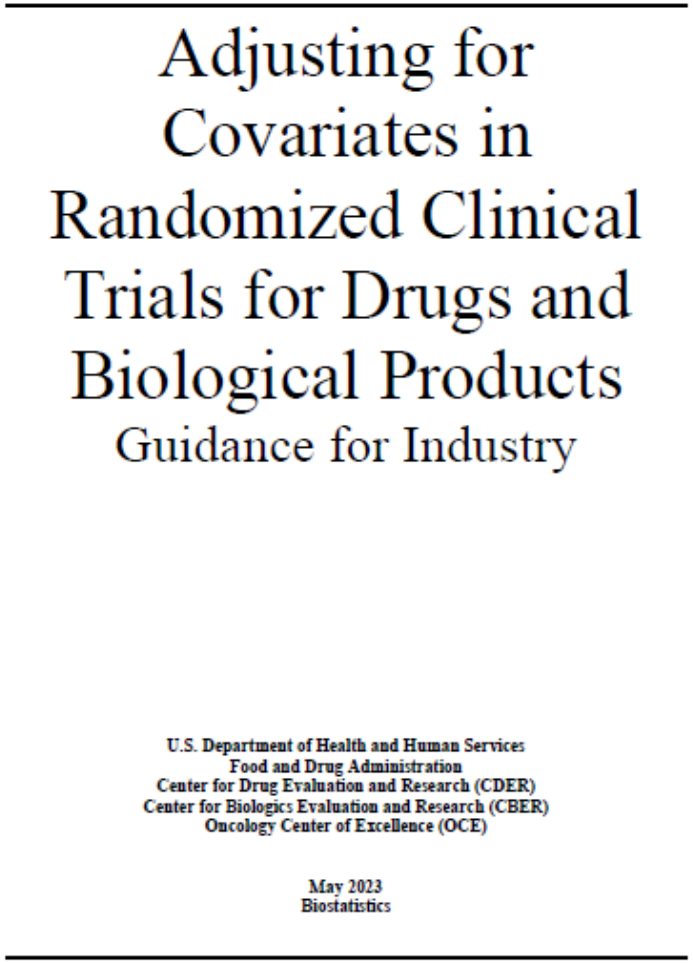
- FDA protects and promotes public health in the United States by regulating human and veterinary drugs, biologic products, medical devices, food, tobacco, and more
- CDER ensures that safe and effective drugs are available
- The Office of Biostatistics (OB) provides statistical leadership, expertise, and advice to support the CDER mission, such as through:
  - Reviews of sponsor submissions throughout drug development programs
  - Research, support for internal and external programs, and development and dissemination of policy and guidance
    - Article in Spring 2024 ASA Biopharmaceutical Report describes OB's approach to developing statistical policy and guidance, including opportunities for external engagement

Brief Updates on Several Statistical Topics

- I will cover several statistical topics that are important and for which there are relevant recent or ongoing policy or guidance efforts
  - Not intended to represent a comprehensive list of important topics
- For each topic, I will:
  - Briefly summarize relevant recent or ongoing policy or guidance efforts, with a focus on providing links to resources for you to read and learn more
  - Describe a few high-level principles related to the topic that I find particularly notable or important

Covariate Adjustment: Updates

- Final FDA guidance on covariate adjustment published in May 2023; the guidance reflects FDA's current recommendations on adjusting for covariates in the statistical analysis of randomized clinical trials in drug development programs



Adjusting for Covariates in Randomized Clinical Trials for Drugs and Biological Products

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)
Oncology Center of Excellence (OCE)

May 2023
Biostatistics

Covariate Adjustment: Notable Principles

- Pre-specified adjustment for baseline covariates in the primary analysis is acceptable and can improve precision and power
- Adjustment for covariates anticipated to be most prognostic of outcome is recommended, but covariate adjustment is acceptable even if covariates are not prognostic or are strongly associated with each other
- Covariate adjustment in a linear model provides valid inference on the average treatment effect even if the model is misspecified and does not accurately capture the relationships with outcome
  - Use of robust (e.g., “sandwich”) standard error method recommended
  - Standard error computation should account for stratified randomization
- Covariate adjustment in a non-linear model involves additional considerations, including whether interest is in a conditional or unconditional treatment effect

Real-World Evidence (RWE): Updates

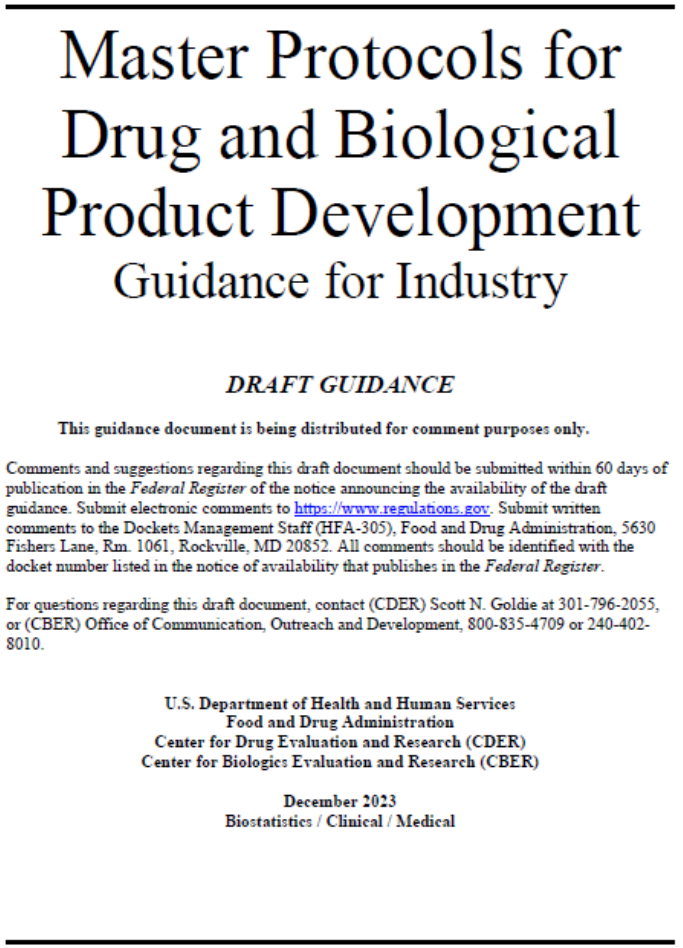
- FDA created a program in 2018 for evaluating the potential use of RWE to support a new indication for an approved drug or to satisfy post-approval study requirements
- FDA published many guidances related to real-world data (RWD) and RWE, e.g.,
  - Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products
  - Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products
  - Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products
  - Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products
- See here for additional information on FDA RWE program and guidances

Real-World Evidence: Notable Principles

- RWD can be leveraged and/or RWE generated for different purposes in the context of different study designs; for example:
  - To inform trial design (e.g., population and endpoint selection, feasibility)
  - Within a randomized controlled trial (e.g., with outcomes collected through electronic health records or claims data)
  - Within an externally controlled trial
  - Within an observational study
- Considerations depend greatly on context of use
- Randomization remains the recommended gold standard for generating reliable information on drug safety and effectiveness
- RWE can play an important role in randomized trials, e.g., with pragmatic elements to increase efficiency, patient centricity, and generalizability
  - e.g., see C3TI demonstration on Streamlined Trials Embedded in Clinical Practice

Master Protocols: Updates

- Draft FDA guidance on master protocols published in December 2023; the guidance provides recommendations on master protocols, with a focus on confirmatory umbrella and platform trials
- Public comments currently under review
  - One notable recurring comment was a request for additional guidance on basket trials



Master Protocols for Drug and Biological Product Development

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Scott N. Goldie at 301-796-2055, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

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)

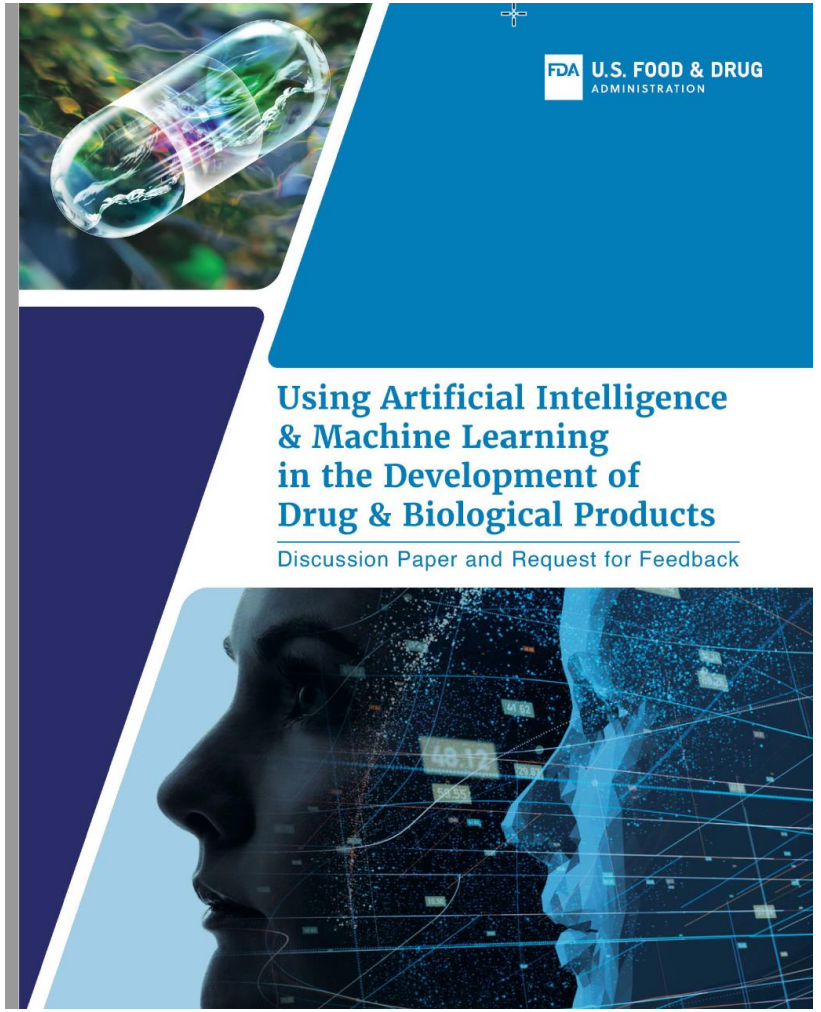
December 2023
Biostatistics / Clinical / Medical

Umbrella and Platform Trials: Notable Principles

- The primary analysis should generally include only concurrent controls unless a compelling justification supports use of non-concurrent controls
- Extra care needed to preserve integrity of randomized comparisons, e.g.,
  - In scenario with some drug-specific eligibility criteria, analyses for given drug should utilize only control subjects who were eligible for and could have been assigned to drug
  - In setting where randomization ratio changes over time (e.g., a ratio of $\sqrt{k}$:1 with k drugs active in a platform trial), comparisons should account for changes
- Different blinding strategies (e.g., partial blinding) may be considered, depending on context
- We do not generally recommend multiplicity adjustments to strongly control Type I error (T1E) probability across multiple comparisons of different drugs
  - Still important to control for multiple comparisons for each individual drug

Artificial Intelligence (AI) and Machine Learning (ML): Updates

- FDA discussion paper on using AI and ML in the development of drug and biological products released in 2023
- FDA discussion paper on artificial intelligence in drug manufacturing also released in 2023

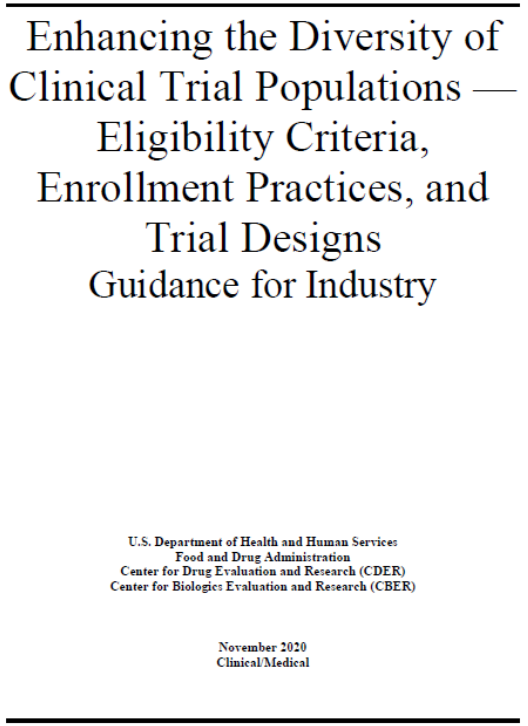


AI and ML: Notable Principles

- Broad range of current and potential uses of AI and ML in drug development and regulation, such as:
  - Drug discovery, nonclinical research, clinical study design and analysis, safety surveillance, manufacturing, regulatory use (e.g., site selection for inspection)
- Key considerations include but not limited to importance of human governance, transparency, reproducibility, and validity
- Risk of use and expected evidence depend on context of use, e.g.,
  - Adjustment for baseline prognostic score derived from external data (e.g., using AI) as covariate in linear model to improve precision and power
    - If model to derive score is fully pre-specified, this is an example of ANCOVA and reasonable
  - Comparison of single-arm trial results to predicted counterfactual outcomes on placebo based on a model derived from external data (e.g., using AI)
    - Much higher risk; validity of inference on treatment effect depends on model performance

Diversity in Clinical Trials: Updates

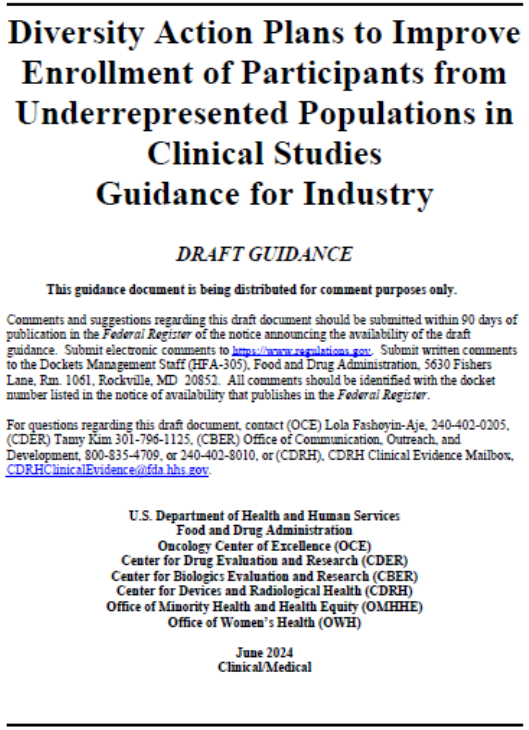
- Final FDA guidance on enhancing the diversity of clinical trial populations published in November 2020
- Draft FDA guidance on Diversity Action Plans to improve enrollment of participants from underrepresented populations in clinical studies published in June 2024



Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs
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 2020
Clinical/Medical



Diversity Action Plans to Improve Enrollment of Participants from Underrepresented Populations in Clinical Studies
Guidance for Industry

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For questions regarding this draft document, contact (OCE) Lola Fashoyin-Aje, 240-402-0205, (CDER) Tanny Kim 301-796-1125, (CBER) Office of Communication, Outreach, and Development, 800-835-4709, or 240-402-8010, or (CDRH), CDRH Clinical Evidence Mailbox, CDRHClinicalEvidence@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence (OCE)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Office of Minority Health and Health Equity (OMHHE)
Office of Women's Health (OWH)

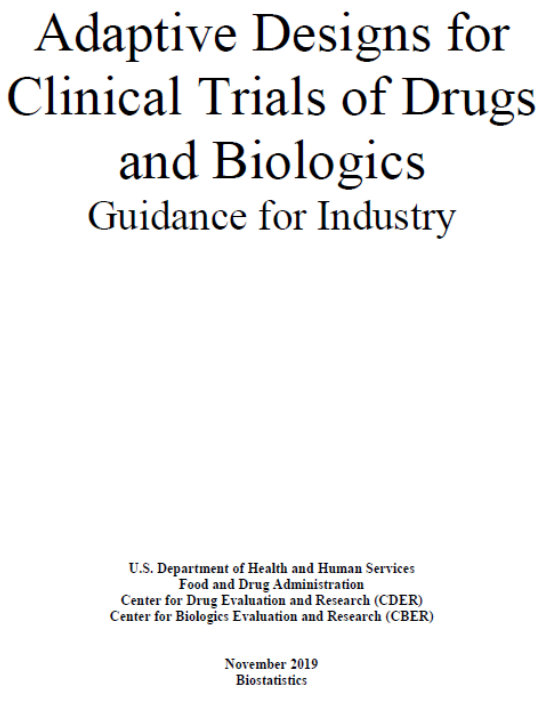
June 2024
Clinical/Medical

Diversity in Clinical Trials: Notable Principles

- Trials should enroll diverse populations that accurately reflect patients likely to take drug if approved
  - Important to ensure generalizability of results and facilitate assessment of differences in safety and effectiveness by relevant patient characteristics
- Examples of approaches to enhance diversity:
  - Examine each exclusion criteria and remove those not necessary to assure safety
  - Utilize inclusive enrollment practices with respect to age, sex, race, ethnicity
  - Make trial participation less burdensome
  - Ensure that clinical trial sites include locations with diverse populations
- Sponsor Diversity Action Plans including enrollment goals for different groups, rationale for goals, and steps to achieve goals can enhance diversity and will be required for phase 3 studies for which enrollment begins after 180 days from publication of a final action plan guidance

Adaptive Designs and CIDs: Updates

- Final FDA guidance on adaptive designs published in 2019
- Final FDA guidance on interacting with FDA on CIDs published in 2020
- FDA CID Meeting Program offers opportunity for increased interaction on proposed CIDs
  - Five case studies described here
- Ongoing work on ICH E20 guideline for adaptive designs and FDA Bayesian guidance

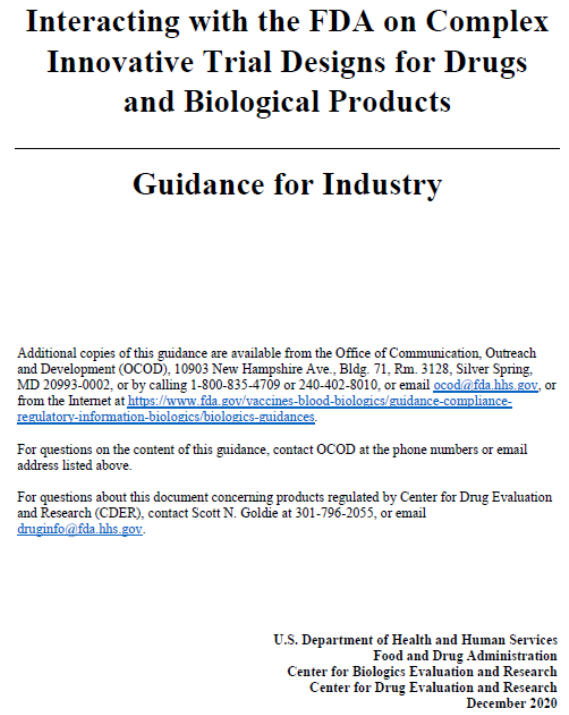


Adaptive Designs for Clinical Trials of Drugs and Biologics

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.

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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

Adaptive Designs and CIDs: Notable Principles

- Key principles for adaptive designs include adequacy of trial planning, control of chance of erroneous conclusions, reliability of estimation, and maintenance of trial integrity, e.g., sponsors should:
  - Pre-specify anticipated adaptation rule (even if not necessary for valid inference)
  - Utilize existing methods (e.g., for group sequential designs) to estimate effects that account for design to reduce bias and mean-squared error
- Early interaction, detailed documentation important for CID proposals
  - Should include discussion of rationale for design and detailed evaluation of operating characteristics (including simulation report, if applicable)
  - Bayesian approaches should include clear, detailed description and justification of choice of prior distribution and decision criteria

Other Topics of Interest

- Principles for the selection of appropriate primary estimands
- Prevention and handling of missing data
- Statistical considerations in the evaluation of surrogate endpoints
- Evaluating heterogeneity of treatment effects
  - Including shrinkage estimation; see FDA Impact Story
- Statistical considerations in rare disease settings
- Statistical engagement and considerations in safety assessment
  - Including topics such as improved planning (e.g., ascertainment strategy), choice of metric (crude proportions vs. alternatives), stratification by trial, estimating uncertainty, on-study vs. on-treatment analysis

Thank you!


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