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
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Outline

- Introduction
- High-level policy and guidance updates on a few topics with important statistical considerations
  - Substantial evidence of effectiveness
  - Bayesian methods
  - Master protocols
  - Adaptive designs and complex innovative designs (CIDs)
- Other topics of interest

Introduction

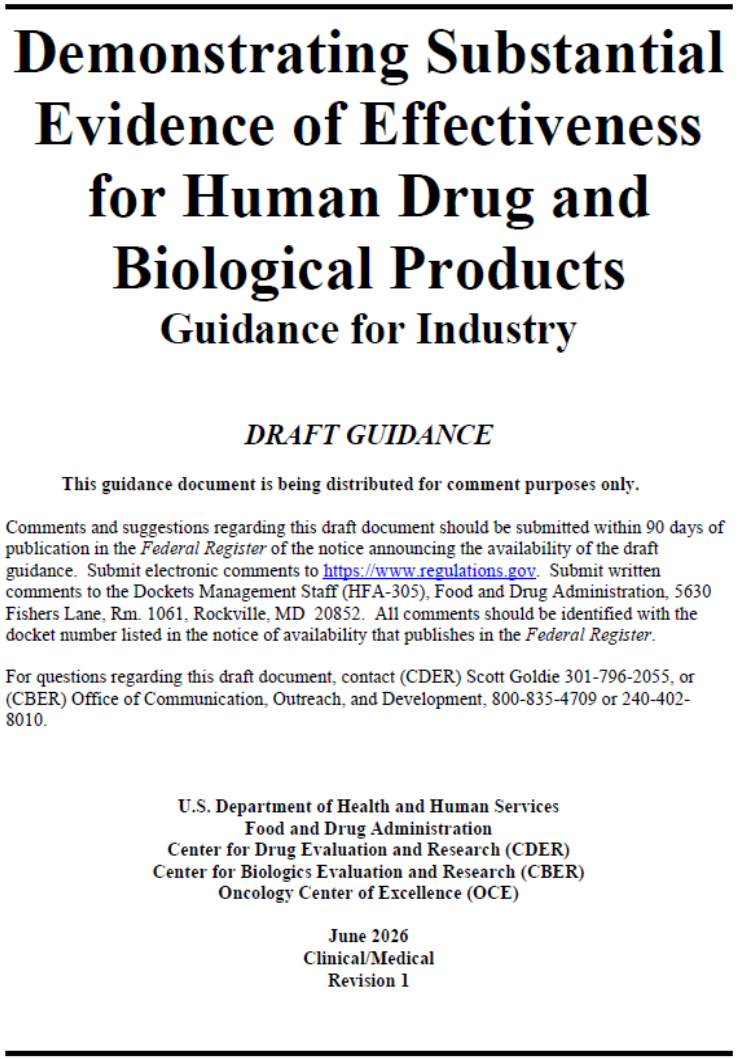
- FDA protects and promotes public health in the United States by regulating human and veterinary drugs, biologic products, medical devices, food, tobacco, and more
- CDER ensures that safe and effective drugs are available
- The Office of Biostatistics (OB) provides statistical leadership, expertise, 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 a Few Important Topics

- I will cover a few topics with important statistical considerations 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

Substantial Evidence of Effectiveness: Updates

- Revised draft FDA guidance on demonstrating substantial evidence of effectiveness published in June 2026
- This draft guidance replaced the previous 2019 draft
- This guidance will replace the 1998 guidance on the topic when it is finalized



Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products

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 90 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 Goldie 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)
Oncology Center of Excellence (OCE)

June 2026
Clinical/Medical
Revision 1

Substantial Evidence of Effectiveness: Background

- U.S. law requires that applicants demonstrate substantial evidence of effectiveness (SEE) to gain marketing approval
- The law defines SEE as evidence from more than one adequate and well-controlled (AWC) study or evidence from one AWC study plus confirmatory evidence
  - Confirmatory evidence may be based on, for example, effectiveness of the drug in related diseases, effectiveness of related drugs, strong mechanistic evidence, etc.
- U.S. regulations characterize important aspects of AWC studies, including a valid choice of control, appropriate participant selection and treatment assignment (e.g., randomization), adequate measures to minimize bias (e.g., blinding), well-defined and reliable endpoints, and appropriate statistical analyses

Substantial Evidence of Effectiveness: Notable Principles and New Developments

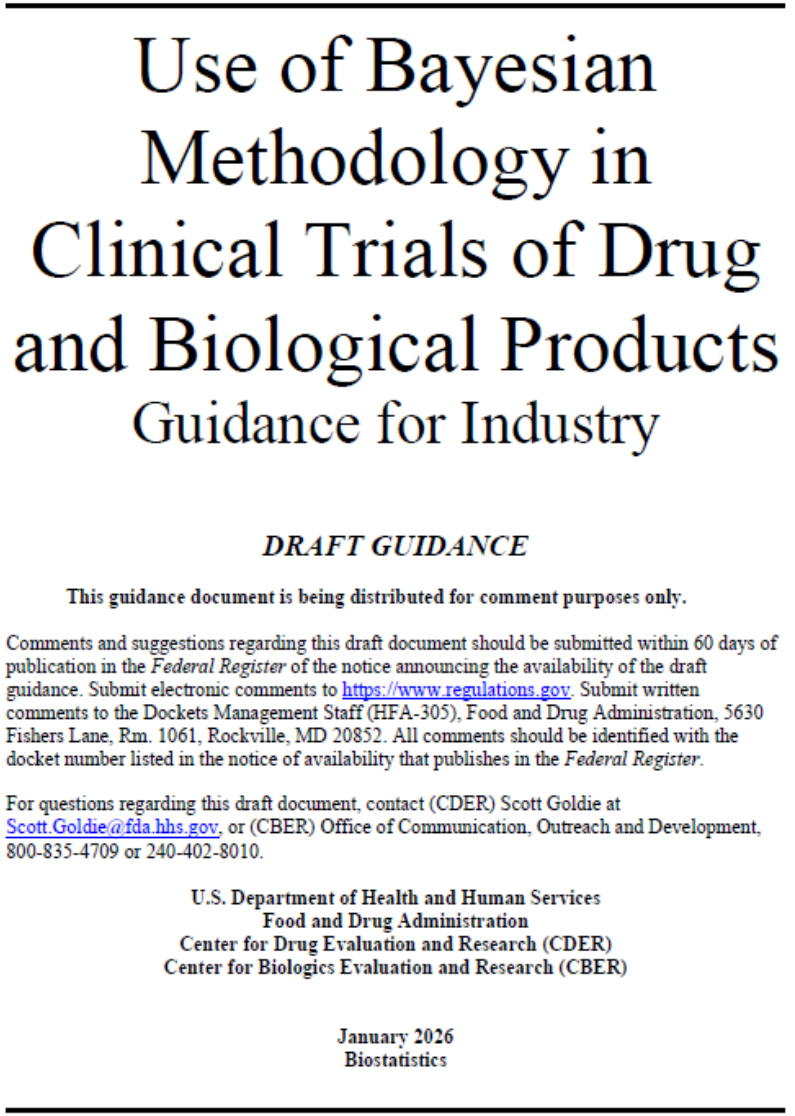
- The revised draft guidance emphasizes that many factors impact the strength of evidence of effectiveness, including elements of study design, conduct, and analysis, the clinical and statistical persuasiveness of results, and aspects of the overall development program
- The guidance provides high-level considerations and recommendations on some important examples of such factors
- Much of this discussion is similar to previous SEE guidance but there is some new content, e.g.,
  - It is important to consider results from *all* relevant studies
  - It is important that designs provide information relevant to clinical practice (e.g., broad eligibility criteria, standard-of-care control arm and supportive therapy)

Substantial Evidence of Effectiveness: Notable Principles and New Developments

- The revised draft guidance continues to support the value of substantiation of results across independent trials but more clearly opens the door to use of one scientifically rigorous trial plus confirmatory evidence across broad settings, not only in settings warranting regulatory flexibility (e.g., rare diseases)
  - This does not mean sponsors can just rely on one trial with a similar design and size as would typically be utilized with two trials; if strong confirmatory evidence is not available, this approach requires a highly persuasive trial
- Sponsors should discuss their anticipated SEE approach with FDA early in development and no later than at an end-of-phase 2 meeting

Bayesian Methods: Updates

- Draft guidance on use of Bayesian methodology in clinical trials published in January 2026
- FDA is currently reviewing public comments on the draft and working on revisions
- FDA is also developing guidance on informative Bayesian methods in pediatric clinical trials



Use of Bayesian Methodology in Clinical Trials of Drug and Biological Products

Guidance for Industry

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
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January 2026
Biostatistics

Bayesian Methods: Some Example Uses (*references to specific examples are in guidance*)

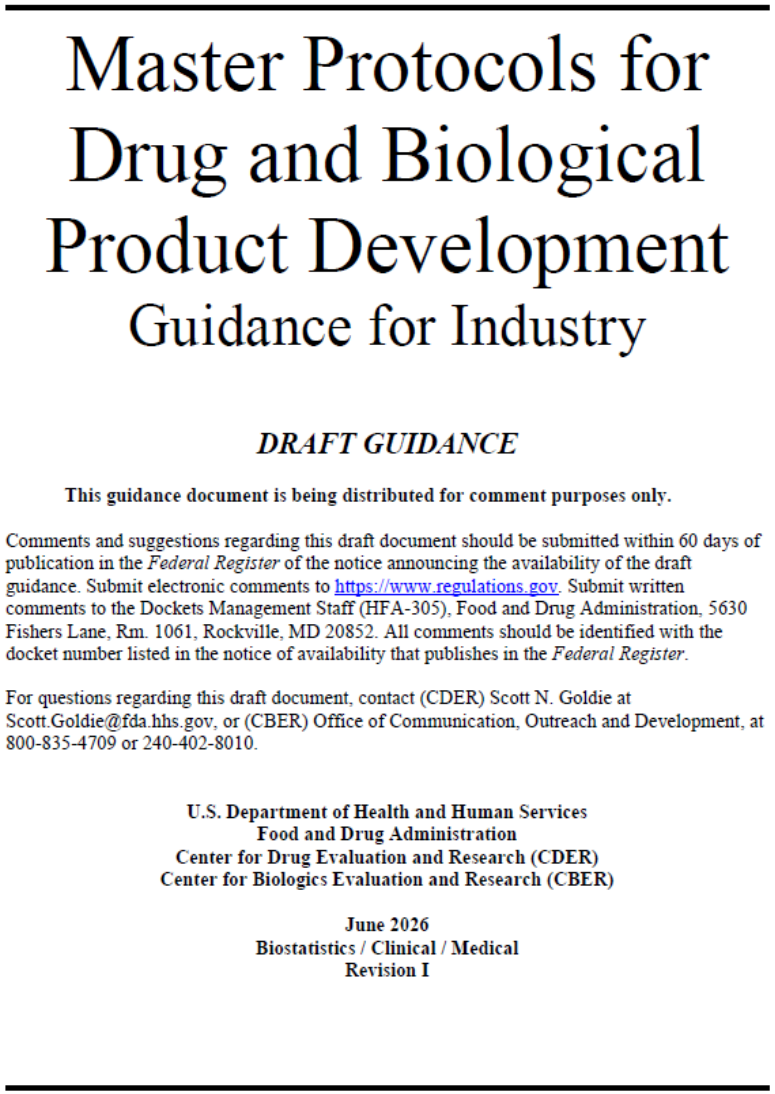
- Borrowing from previous trials
- Augmenting a randomized concurrent control using an external control or nonconcurrent control
- Pediatric extrapolation
- Borrowing information across similar diseases or disease subtypes
- Borrowing information between subgroups of a patient population
- Dose-finding trials in oncology
- Complex adaptive designs

Bayesian Methods: Notable Principles

- In trials with Bayesian inference for the primary estimand, typical success criteria (chosen to control the type I error rate at 2.5%) may not be applicable or appropriate, so careful specification of alternative success criteria (e.g., based on posterior probability) is often critical
- Sponsors should prespecify and justify full details of the prior distribution
- Use of informative priors that borrow external information generally require greater justification and additional considerations, such as:
  - Identification and review of all available relevant external information
  - Evaluation of how much to leverage external information
  - Construction of a specific prior (e.g., considering assumptions, influence, discounting, etc.)

Master Protocols: Updates

- Revised draft FDA guidance on master protocols published in June 2026, replacing the previous 2023 draft guidance
- One notable change to address public comments on the previous draft is the addition of considerations and recommendations on basket trials



Master Protocols for Drug and Biological Product Development

Guidance for Industry

DRAFT GUIDANCE

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Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
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June 2026
Biostatistics / Clinical / Medical
Revision I

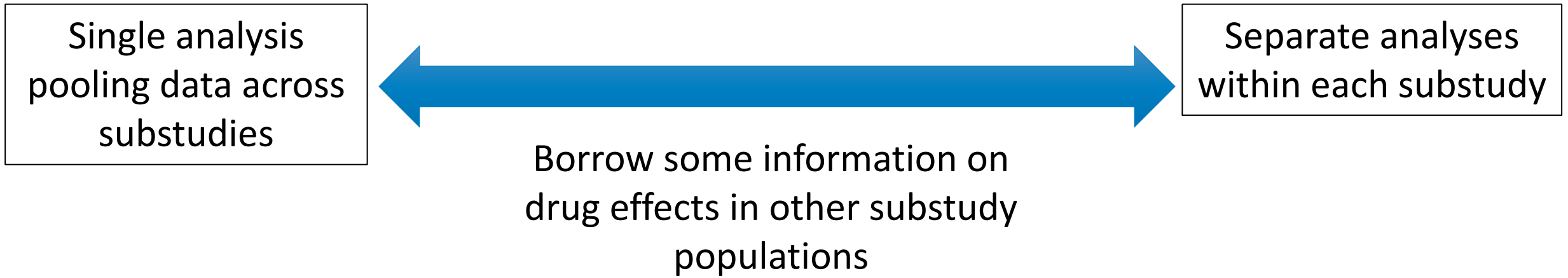
Umbrella and Platform Trials: Notable Principles

- 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 √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
- FDA does 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

Basket Trials: Notable Principles

- In settings where there is sufficient scientific justification, sponsors may consider leveraging information across related substudy populations to allow for potential efficiency gains
- Considerations on when and how much to leverage information include:
  - The extent to which drug effects are expected to be similar across the substudy populations, which may be influenced by the degree of similarity in disease pathophysiology, pharmacology, and endpoints and other estimand attributes
  - The prevalence of the different populations and feasibility considerations
  - If there will be additional late-phase trial(s) to contribute to evidence of effectiveness

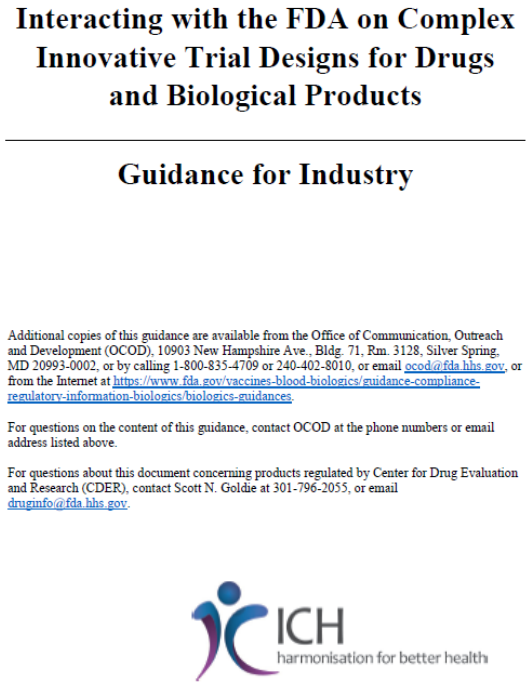
Continuum of Analysis Approaches



Bias-variance tradeoff: increases in borrowing generally improves precision and power, but also may increase bias in the evaluation of drug effects in a given substudy population

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 increased interaction on CIDs
  - Six case studies described here
  - In 2028, CID program will be incorporated into standard review practice (see PFUFA VIII commitment letter)
- Draft ICH E20 guideline on adaptive designs published in 2025; ongoing work to address public comments and develop final guideline



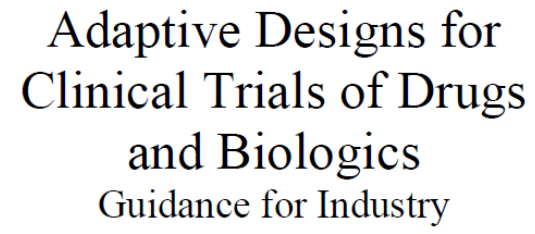
Interacting with the FDA on Complex Innovative Trial Designs for Drugs and Biological Products

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.



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)
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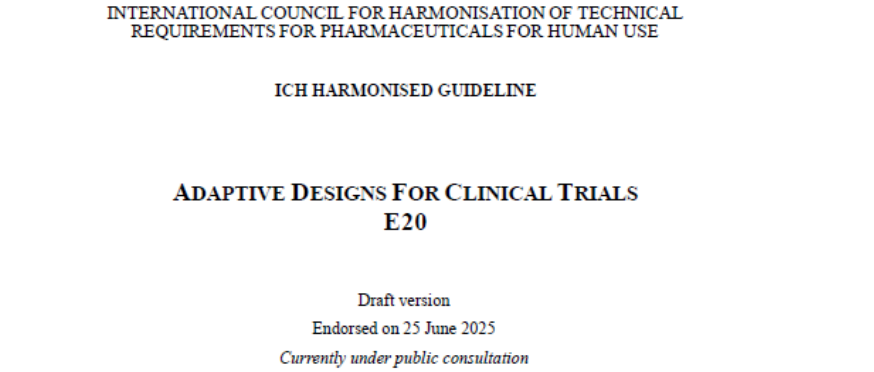
November 2019
Biostatistics



INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

ADAPTIVE DESIGNS FOR CLINICAL TRIALS
E20

Draft version
Endorsed on 25 June 2025
Currently under public consultation

Adaptive Designs and CIDs: Notable Principles

- Key principles for adaptive designs include the adequacy within the development program, adequacy of trial planning, control of the 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)

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
- 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

** See plans for guidance on some of these topics in 2026 CDER Guidance Agenda*

Thank you!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