

FDA's Implementation of the Estimand Framework and Complex Innovative Trial Design Meeting Program

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Learning Objectives

1. Describe the five attributes of an estimand
2. Discuss the role of intercurrent events in clinical trial planning
3. Identify key aspects of complex innovative trial designs
4. Explain how to initiate interaction with FDA on a complex innovative trial design proposal through the CID Meeting Program

Part 1

Estimand Framework: Background and Implementation

Background: Missing data



- Missing data long recognized as a problem in medical studies
- If observations are unavailable for reasons hypothetically related to their values, can lead to biased estimates, erroneous decisions
- Even if observations are missing completely at random, missing data reduces power / precision
- FDA launched effort to address missing data in clinical trials in 2008 (PDUFA IV commitment)

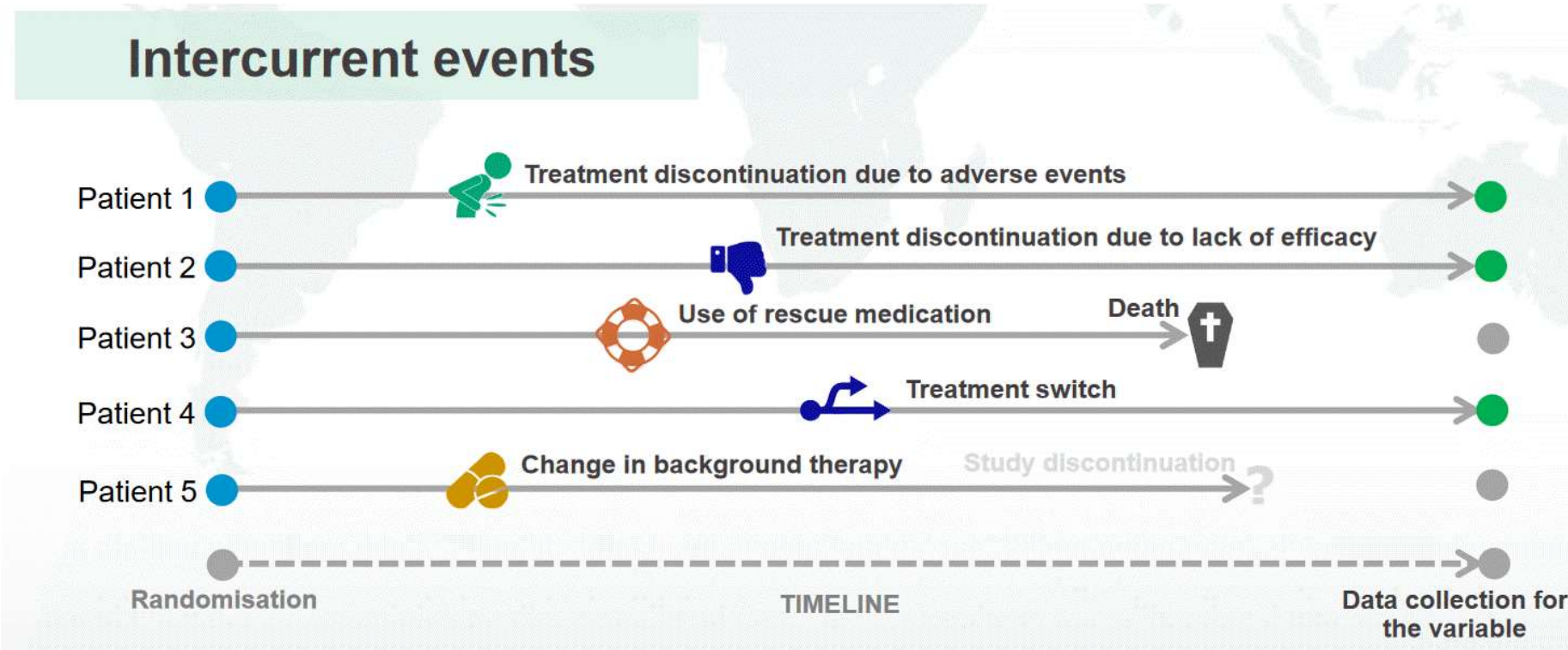
Missing vs. meaningless data



- Suppose we're investigating a treatment for pain
- We design a trial with week 12 pain score as the primary endpoint
 - If a subject drops out of the study at week 8, they have a pain score at week 12, we just don't know it
 - If a subject dies at week 8, they do not have a pain score at week 12, it's a meaningless concept
- Death in this example is an *intercurrent event*

Intercurrent events

Intercurrent events



Intercurrent events and treatment effect



Some patients will require additional medication, others will not.
This creates different potential choices of treatment effect of interest



... regardless of whether **additional medication** is used.

or

... in the hypothetical condition that **additional medication** was not available.

or

... in the stratum of this population that does not require **additional medication**.



The underlying problem

- Many trials have had vague objectives such as “showing efficacy”
 - Leads to ambiguity in how to handle missing data
 - Raises barriers to communication
- What’s needed is a more precise statement of the exact treatment effect we’re trying to measure
 - The estimand

Some terminology

- *Estimand* is the thing you want to estimate
 - A concept, such as treatment effect
 - Should flow from the overall study objective
- *Estimator* is the statistic you use to estimate the estimand
 - A mathematical procedure, such as arithmetic mean
- *Estimate* is the specific value of the estimator applied to your data
 - A number, such as 42, or 18%

ICH E9(R1)

E9(R1) STATISTICAL PRINCIPLES
FOR CLINICAL TRIALS:
ADDENDUM: ESTIMANDS AND
SENSITIVITY ANALYSIS IN
CLINICAL TRIALS
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)

May 2021
ICH

Revision 1

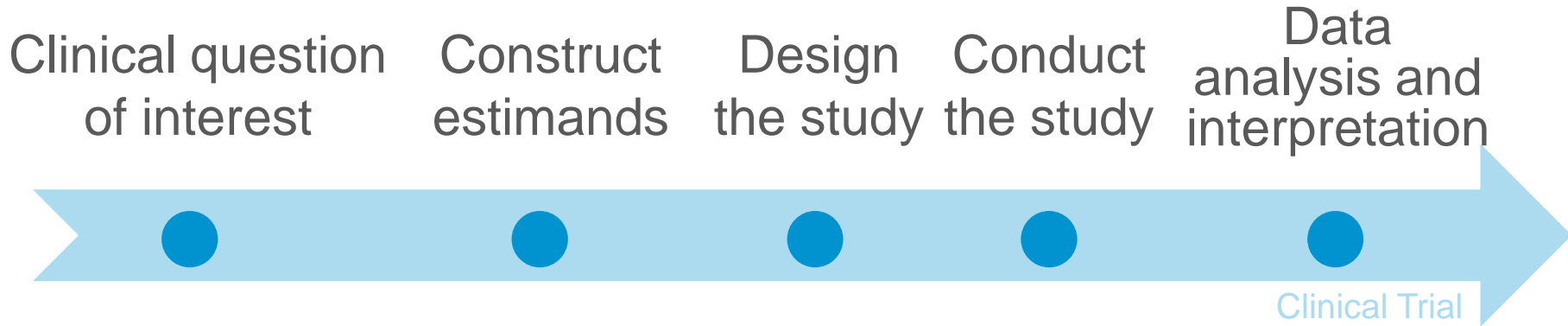
- ICH E9(R1) is an addendum to ICH E9
- Introduces the estimand framework
- Encourages sponsors to be specific about:
 - What treatment effect, exactly, do we care about?
 - How do we estimate it?

ICH E9(R1)



- Defines estimand as a precise [numerical] characterization of the treatment effect at the population level
- Aligns clinical questions, study objectives, design, conduct, data collection, analysis
- Explicitly addresses intercurrent events in defining clinical questions and the treatment effect and distinguishes them from missing data
- Clarifies definitions of sensitivity and supplementary analyses

Estimands in the trial design process



- Study objectives flow from the clinical question of interest
- Estimands flow from objectives
 - Also serve as detailed, specific statements of objective

Estimand attributes

Treatment



Population



Variable



Intercurrent events



Population-level summary



Treatment

- The *treatment* attribute covers the treatment condition of interest and alternative treatment to which comparison will be made
- Treatment attributes includes:
 - Dose, regimen, route
 - Background care (e.g., investigational + standard of care vs. standard of care alone)
 - Allowed concomitant or rescue medications

Population

- The *population* attribute covers:
 - Patients targeted by the clinical question
- Should be specific, may include:
 - Diagnosis
 - Age or other demographic info
 - Baseline clinical characteristics, prognostic factors

Variable (or endpoint)

- The *variable* attribute covers:
 - The variable or endpoint to be collected for each subject to address the clinical question of interest

Intercurrent events

- Intercurrent events [ICEs]:

Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest. It is necessary to address intercurrent events when describing the clinical question of interest in order to precisely define the treatment effect that is to be estimated.

- Intercurrent events happen in clinical practice as well as trials
Should be approached respectfully as meaningful parts of a patient's journey, not dismissed as statistical nuisance
- Potential ICEs should be identified and a strategy proposed for each

Intercurrent event strategies

- A *strategy* reflects the choice made on how to address intercurrent events, in order to describe the treatment effect that is targeted
- ICH E9(R1) identified 5 strategies:
 - Treatment policy
 - Composite
 - Hypothetical
 - Principal stratum
 - While-on-treatment

Strategy: Treatment policy



- The treatment policy strategy treats the ICE as if it does not change the interpretation of the variable
- Data collected for variable are used regardless of occurrence of ICE
- Cannot be used for terminal events (e.g. death, surgery)

Strategy: Composite

- The composite strategy identifies the ICE as an important clinical event that informs the effectiveness of the treatment
- The occurrence of the ICE becomes part of the variable

Strategy: Hypothetical

- The hypothetical strategy is based on imagining a situation in which the ICE would not have occurred
- The variable's value is set to be the value it would have taken had the ICE not occurred
- Several important considerations:
 - The hypothetical situation has to be *specific*
 - The hypothetical situation has to be *relevant*
 - The imputation strategy has to be *sound and reliable*

Strategy: Principal stratum

- The principal stratum strategy typically seeks to answer the scientific question of interest in the population of patients for whom the ICE would not (or would) occur on either treatment arm
 - Note: not the same as the subset of patients in whom the ICE *did not occur*
- Usually requires strong assumptions

Strategy: While-on-treatment



- The while-on-treatment strategy addresses the scientific question of treatment effect prior to the occurrence of the ICE
- Defines the variable as the measured value until the ICE occurs
- In general, this may mean different duration of treatment for different patients

Strategies example: Rescue medication

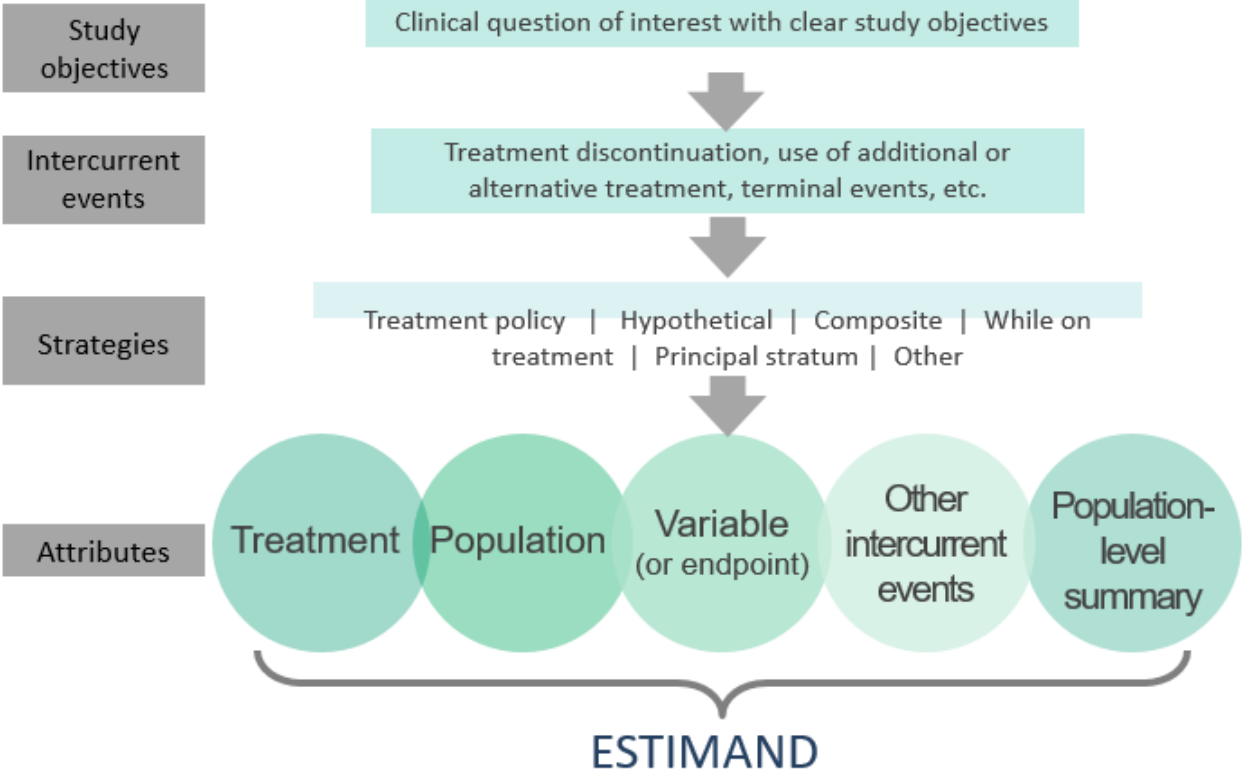


- Treatment policy: Treat rescue as part of treatment attribute
- Composite: Treat rescue as part of endpoint (i.e., a failure)
- While-on-treatment: Measure symptoms up to rescue
- Hypothetical: Assess effect if rescue weren't available
- Principal stratum: Assess effect in patients who would not need rescue in either arm

Population-level summary

- The *population-level summary* attribute provides a basis for comparing treatment conditions
- Examples:
 - Difference in mean change over time
 - Ratio of proportion of patients responding
 - Hazard ratio

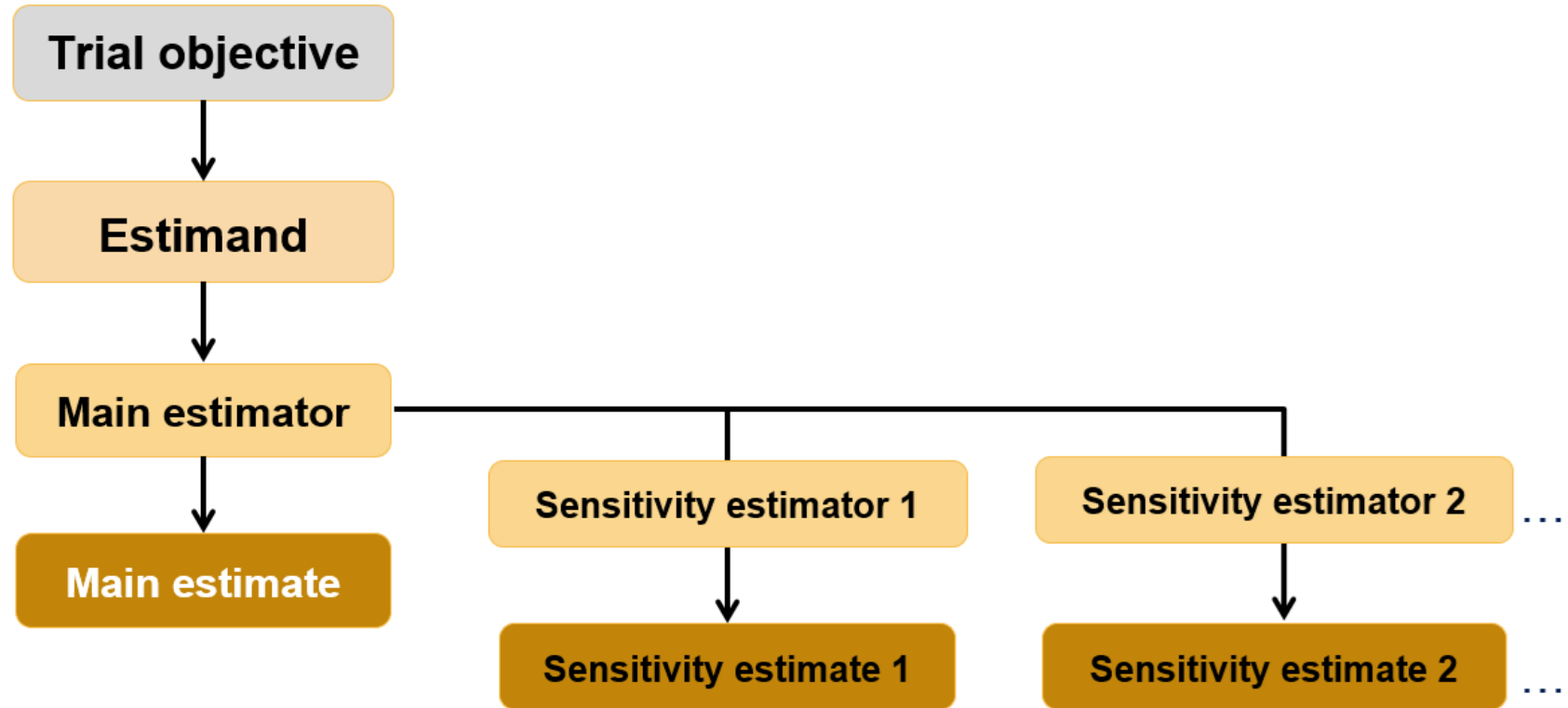
Bringing it together



Missing data

- ICH E9(R1) distinguishes between data that are not meaningful due to an intercurrent event and *missing data*
- Missing data are:
Data that would be meaningful for the analysis of a given estimand but were not collected. They should be distinguished from data that do not exist or data that are not considered meaningful because of an intercurrent event.
- Missing data will often be the cause of sensitivity analyses

Sensitivity analyses



Estimand resources

- [Guidance for Industry: E9\(R1\) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials](#)
- [ICH E9\(R1\) training material](#)
- [Clinical and Statistical Perspectives on the ICH E9\(R1\) Estimand Framework Implementation](#)

Challenge Question #1

Which of the following is **not an estimand attribute?**

- A. Variable (or endpoint)
- B. Intercurrent events
- C. Blinding
- D. Population-level summary



Part 2

FDA's Complex Innovative Trial Design Meeting Program

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
- Considerable interest in innovative approaches to increase trial efficiency
 - Adaptive designs
 - Bayesian approaches
 - Incorporating external data

Barriers to innovation

- Due to cost and risk, sponsors sometimes reluctant to experiment with novel trial approaches
- Regulators sometimes resistant to change because of risk of bias / Type I error
- When innovative approaches are accepted, information is often non-public
- Need for innovation is especially critical in rare, serious and life-threatening diseases



CID Meeting Program motivation

- For sponsors, success with an innovative proposal may need:
 - Robust regulatory feedback
 - High-level buy-in
- For FDA, wider use of innovative designs needs case studies that we can talk about publicly
- The CID Meeting Program was formed in collaboration between FDA and industry representatives
 - Part of User Fee Act commitments (PDUFA VI, 2017; PDUFA VII, 2022)

CID review program



- Joint effort between FDA's Center for Drugs (CDER) and Center for Biologics Evaluation and Research (CBER)
- Sponsors submit designs and have the opportunity to engage with regulatory staff via two additional meetings
- FDA selects up to 2 submissions per quarter and 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
- Started as five-year PDUFA VI pilot program; now five-year PDUFA VII Meeting Program

Eligibility criteria

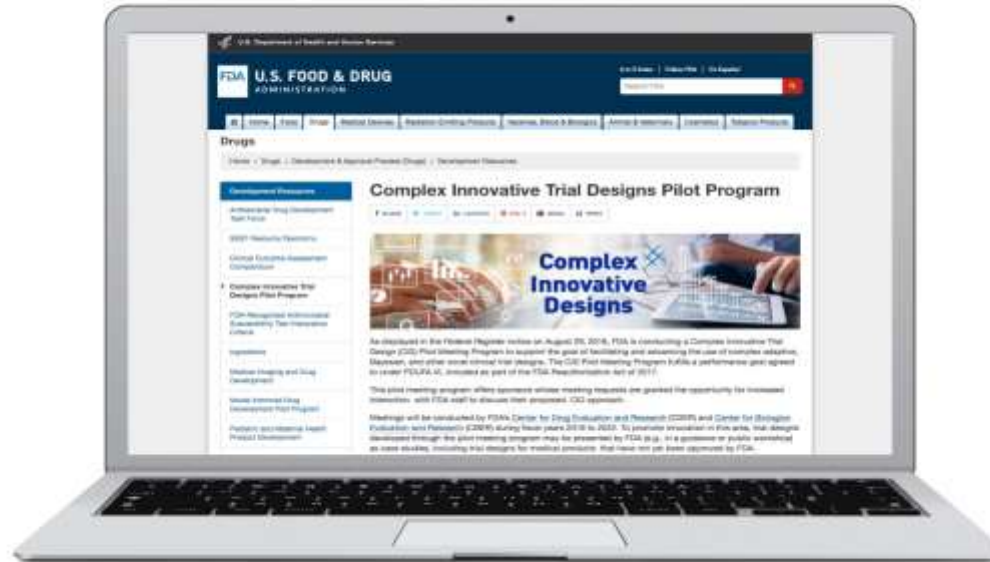


- The sponsor must have a pre-IND or IND number for the medical product(s) included in the CID proposal
- The proposed CID is intended to provide substantial evidence of effectiveness to support regulatory approval of the medical product
- The trial is not a first in human study and there is sufficient clinical information available to inform the proposed CID
- The sponsor and FDA can reach agreement on the trial design information to be publicly disclosed

Evaluation of proposals

- Need for simulations to assess trial design operating characteristics
- Therapeutic need
- Trial design appropriateness for program
- Level of innovation of the trial design

Website



<https://www.fda.gov/CIDpilot>

Case example 1: Duchenne muscular dystrophy

- Duchenne muscular dystrophy is a rare, serious progressive neurological condition
- Primarily affects boys, with rapidly advancing muscle weakness beginning <5 y.o.
- Associated with severe disability, morbidity, and early mortality (usually before age 30)
- Development challenges: small population, difficult short-term endpoint ascertainment

Case example 1: Design



- Randomized, double-blind, placebo-controlled, phase 2/3 trial
- Primary endpoint change in dystrophin levels from baseline to a specified timepoint
 - Important secondary endpoint: Change from baseline in a clinical outcome assessment
- Endpoints analyzed via a Bayesian repeated measures model with multiple interim analyses

Case example 1: Features

- Bayesian adaptive design with the following potential adaptations:
 - Stop the trial for efficacy or safety
 - Modify the sample size
 - Drop an arm
 - Pool doses
 - Change randomization ratio
- Also proposed to explore placebo augmentation with historical controls
- Regulatory discussions focused on areas needing clarification and simulation space

Case example 2: Pediatric MS



- Multiple sclerosis is usually diagnosed in adulthood; 3-5% of MS patients are diagnosed <16 y.o.
- Children diagnosed with MS may have frequent relapses and be more likely to experience cognitive symptoms than adults with MS
- Development challenges: small population, heterogeneous outcomes

Case example 2: Design



- Randomized, double-blind, group sequential, non-inferiority [NI] trial
- Bayesian framework utilizing meta-analytic predictive priors to leverage information from external adult and pediatric studies
- Regulatory discussions focused on NI margin, scope of search for external databases, additional operating characteristic simulations

Case example 3: Chronic pain



- Randomized, double-blind, placebo-controlled, master protocol to evaluate multiple interventions across multiple pain conditions
- Primary endpoint: pain relief from baseline
- Bayesian mixed-model repeated measures analysis with:
 - Borrowing patient information from placebo groups within a pain condition
 - Borrowing treatment effect information across pain conditions for a given intervention

Case example 3: Features

- Possible adaptations
 - Stop for futility
 - Modify sample size
 - Add or remove arms
- Regulatory discussions focused on:
 - Potential drift in placebo response
 - Exchangeability assumptions across pain conditions
 - Missing data frequently encountered in chronic pain trials

Next steps

- Several commitments on CID under PDUFA VII (10/22 – 9/27):
 - Continue the paired meeting program
 - Continue to develop staff capacity to review complex adaptive, Bayesian, and other novel trial designs
 - Hold a public workshop on these topics (by March, 2024)
 - Issue a guidance document on the Use of Bayesian Methodology in Clinical Trials of Drugs and Biologics



CID Resources

- [Complex Innovative Trial Design Meeting Program](#)
- Case studies:
 - [Lupus](#)
 - [DLBCL](#)
 - [Chronic pain](#)
- [Interacting with FDA on Complex Innovative Trial Designs for Drugs and Biological Products](#)
- [Adaptive Design Clinical Trials for Drugs and Biologics Guidance for Industry](#)
- [The U.S. Food and Drug Administration's Complex Innovative Trial Design Pilot Meeting Program: Progress to date](#)

Challenge Question #2

True or false: The FDA has accepted Bayesian and adaptive designs for Phase 3 trials.

- A. True
- B. False

Summary



- Estimands:
 - FDA is encouraging adoption of the estimand framework, particularly for confirmatory trials
 - The estimand framework facilitates clear communication about trial objectives and analyses
- CID program:
 - The FDA is committed to promoting the appropriate use of complex innovative trial designs to improve drug development
 - Sponsors with design proposals can submit them for consideration to the CID Meeting Program

Questions?

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