Clinical Perspectives on Estimand Framework Implementation

EFSPI Regulatory Statistics Workshop 2024
September 11, 2024

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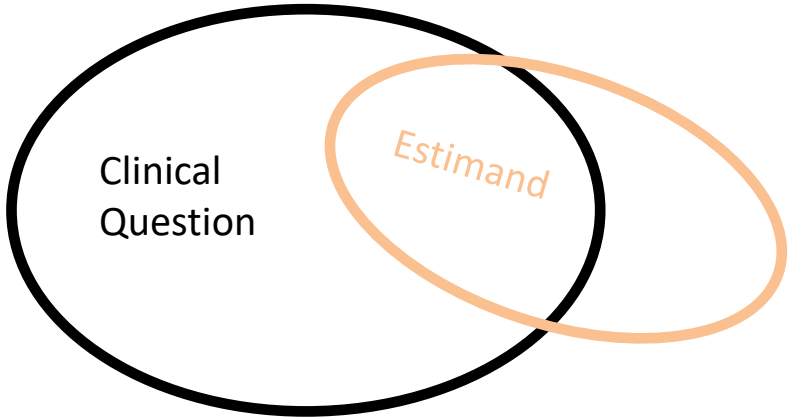
Outline

- Benefits of productive interdisciplinary collaboration
- Challenges of implementing the estimand framework and discussing the clinical question of interest
- Impact of estimand framework on regulatory processes

Clinicians Role in Estimands

- Estimand describes treatment effect of interest, aligning with clinical question

From this…



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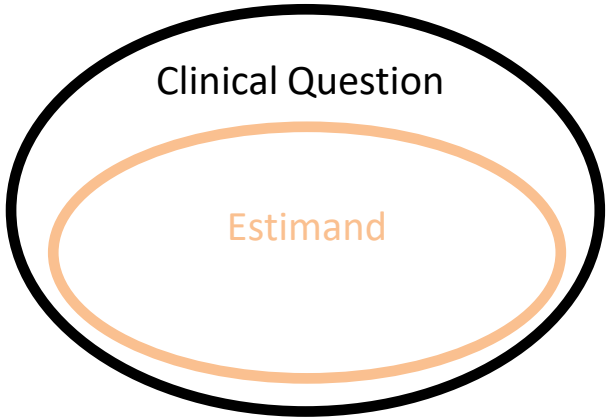
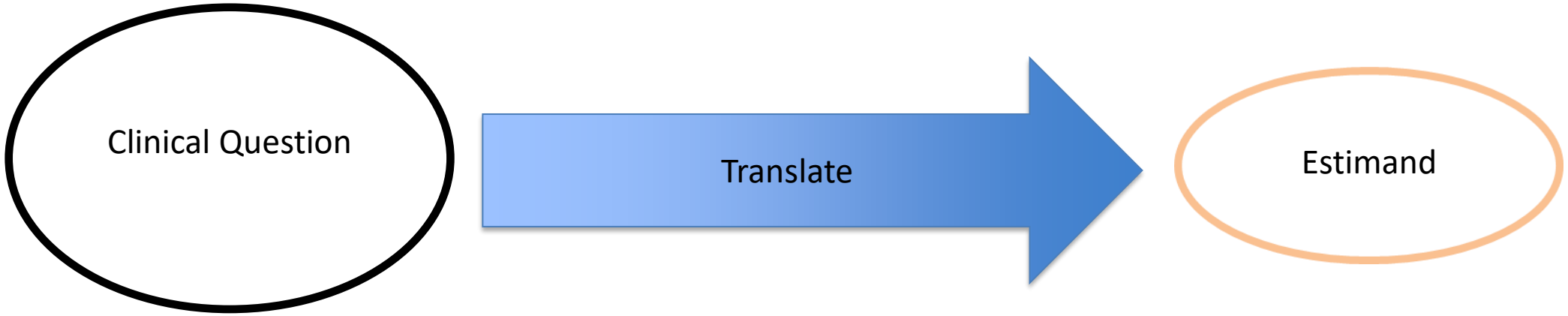


- Goal is to account for intercurrent events that occur after random assignment that may affect assessment of treatment effect
- Common language for addressing varied patient “journeys”
- Helps define benefits and risks of treatment

Engagement Between Clinicians and Statisticians

- Clinicians and statisticians work together to translate the clinical questions into the estimand



- Clinicians assist in identifying clinical question of interest
- Statisticians clearly define estimand terminology to lay a foundation for efficient discussions and aid in translating to estimand

Challenges

- Clear understanding of estimand terminology – knowledge gap
  - Clinicians learning estimand terminology, statisticians learning clinical context creates a more nuanced understanding on how to address intercurrent events
- Each therapeutic area and development program introduces new challenges
  - Implementing composite strategy to reflect an unfavorable outcome on continuous endpoints
- Learn as we go
  - Explore effects of intercurrent event strategies in supplementary analyses to inform future trials

Translate Estimand Terminology

- Clinicians may be more comfortable with more familiar strategies (treatment policy and composite), but not with all strategies
- Helpful to tie back to more familiar terms like ITT
- Useful to decipher between missing data handling vs. ICE strategies
- Ask questions regarding appropriate strategies by framing within the clinical question

Reframe the Strategy into a Clinical Question

Restate each intercurrent event strategy in the form of a clinical question and provide examples

Treatment policy -

- **What is the effect of the test treatment compared to control, regardless of whether the ICE occurred?**
- **Example: When treatment discontinuation occurs, would you be interested in knowing the effect of the drug compared to control regardless of whether treatment discontinuation occurred?**

Composite

- **What is the effect of the test treatment compared to control, reflecting an unfavorable nature of the ICE on the interpretation of the outcome?**
- **Example: If death was the ICE, would you want the death to be reflected in the endpoint assessment? If most subjects died in the trial, but the effect was only assessed in subjects that lived, would that reflect the clinical question?**

Each Therapeutic Area and Development Program Introduces New Challenges

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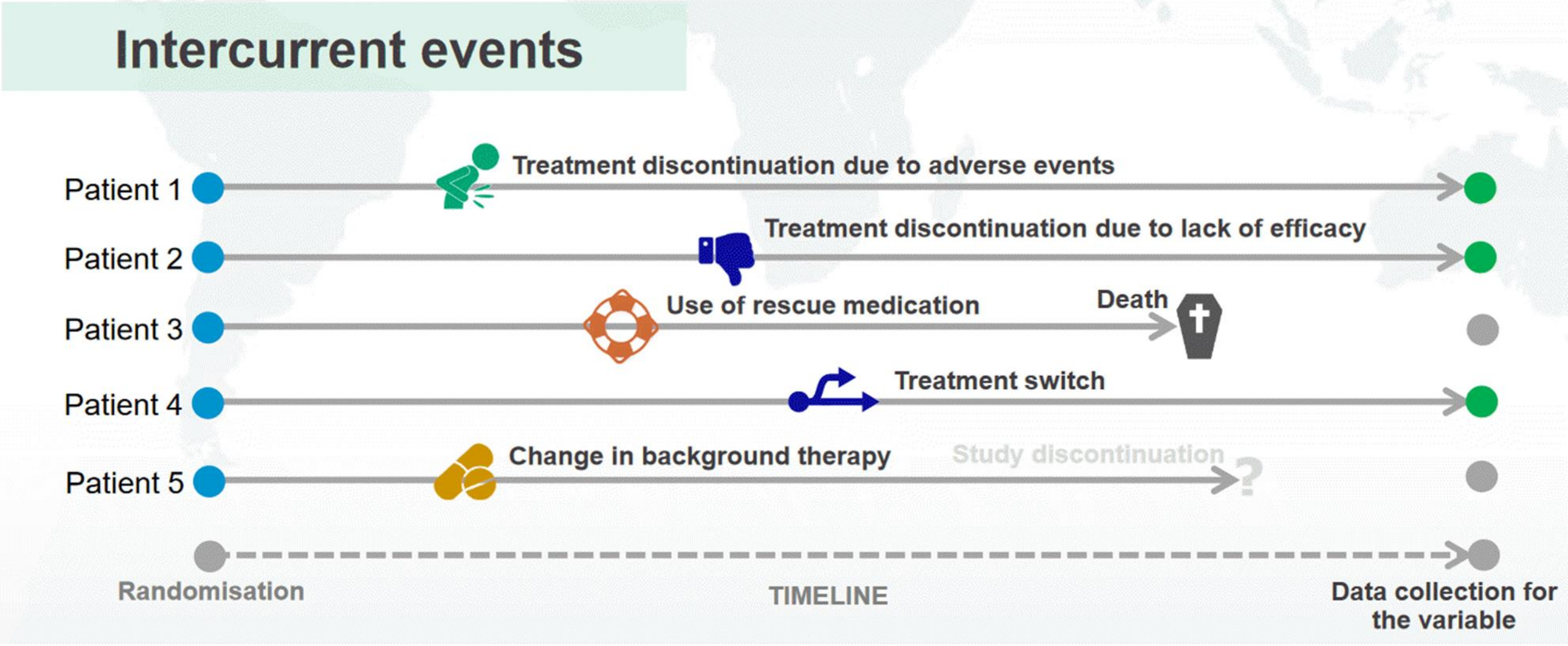


Treatment Discontinuations Can Be Complex

- Consider differentiating treatment discontinuation ICEs by reason for discontinuation
  - Challenges in identifying reason for discontinuation
  - Intercurrent events can overlap
    - Patient can discontinue treatment due to lack of efficacy and undergo a treatment switch

Consider All Relevant Intercurrent Events for the Patient Journey

- Identifying relevant intercurrent event requires knowledge of the patient 'journey'
- Clinical interpretation to identify intercurrent events considered to be treatment failures

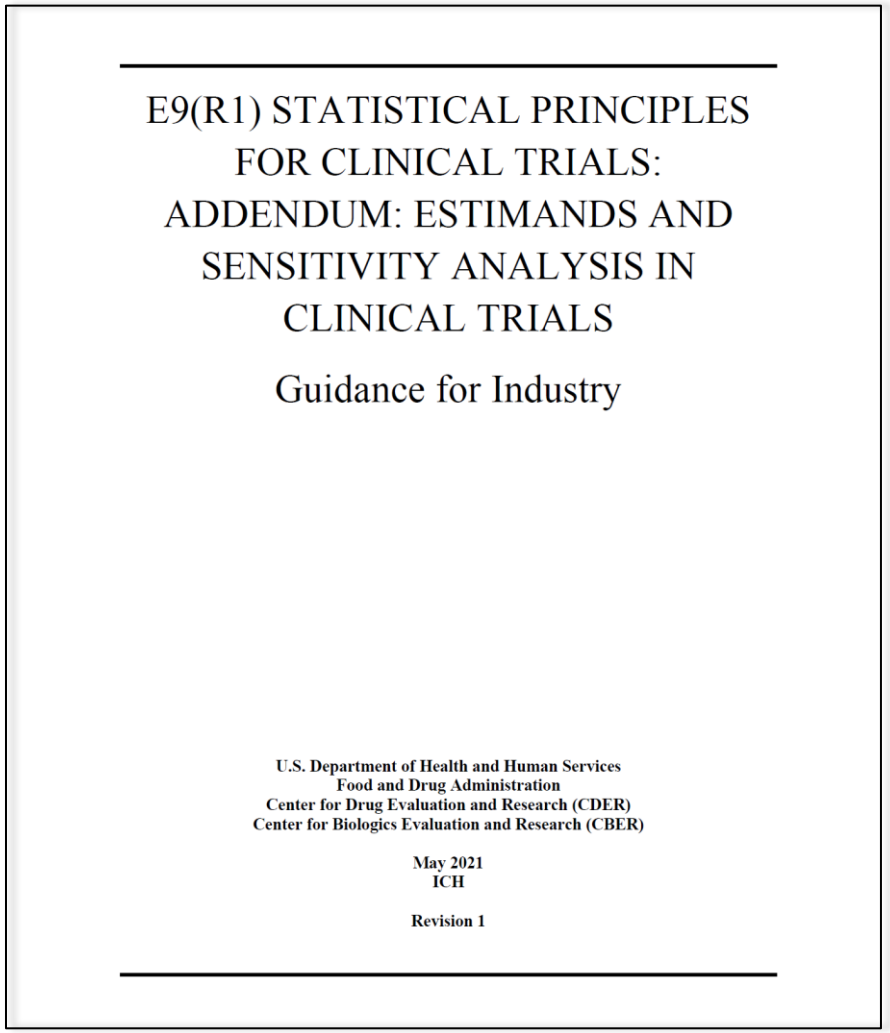
Strategy Implementation is Complex

- Treatment policy
  - Can be complicated if high amount of missing data
- Composite
  - Choice of assigned score is challenging for continuous endpoints
- Hypothetical
  - Uncertainty in ascertaining whether the situation where ICE would not occur is specific and relevant
  - Assessing whether imputation strategy is sound and reliable may not be clear

- Explore effects of ICE strategies in supplementary analyses

Impact of Estimand Framework on Regulatory Process

- Estimands can have a direct impact on both drug approval and labeling claims
- Goal: Derive clinically meaningful and statistically appropriate estimands to discuss with sponsors more effectively and efficiently
- Published Estimands Guidance May 2021
  - Guidance: E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials[1]



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

1: https://www.fda.gov/media/148473/download

FDA Estimand Implementation

Estimands are included in several FDA disease specific guidances

- Estimands included in clinical and statistic review templates
- CDER Estimand working group

Eosinophilic esophagitis
Acute Myeloid Leukemia
Chronic rhinosinusitis w/nasal polyps
Acromegaly*
Diabetic foot infections*
Endogenous Cushing's Syndrome*
Graft-vs-Host Diseases*

* Draft guidance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