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Estimands and Missing Data Working Group

ISCTM Spring Meeting

Feb 19, 2019

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Outline

- Objectives of this working group
- Background:
  - ICH E9(R1) Addendum
  - Defining estimands for a trial
  - Components of an estimand
- Examples of Estimands for Major Depressive Disorder
- Summary of discussion points and wrap-up

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Estimands and Missing Data Working Group (2016 -)

- Objective: develop an approach to the process of applying the estimand framework that will be relevant to many types of studies across clinical areas and illustrate the approach with examples of specific Central Nervous System (CNS) studies.

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ICH E9(R1) Addendum - Background

- Draft ICH E9(R1) Addendum on "Estimands and Sensitivity Analysis in Clinical Trials" released in 2017
- Consultation period ended in May 2018; finalization by end of 2019 or 2020
- Extensive training material (>200 slides) released

  www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html#9-2
- Next steps:
  - Increasing Pharma-regulatory interactions and requests
  - Estimand working groups
  - Papers and case studies
  - Implementation across all clinical trials

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Stakeholders for a Clinical Trial

- Regulatory
- Sponsor
- Prescribers
- Patients
- Payers

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Overall Trial Planning Process

- Trial objective
- Stakeholders for the trial, each with corresponding estimands
- Most appropriate study design
- Estimators (statistical analyses) for each estimand
  - Main estimator
  - Sensitivity estimators

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Process for Each Estimand Definition

- State the stakeholder for whom the estimand is being defined
- Identify the estimand objective, consisting of:
  - the scientific question of interest that the estimand addresses
  - the utility (or purpose) of the estimand for the stakeholder (i.e. how the estimand addresses the needs of the stakeholder).
- Identify the applicable intercurrent events
- Define the four components of the estimand

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Estimand Components

- Population - subjects targeted by the scientific question
- Variable - quantity required to address the scientific question
- Intercurrent events and their corresponding strategies- how to account for each intercurrent event
- Summary measure - the population-level summary for the variable, providing the basis for the treatment comparison.

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ICH E9(R1) Identified Strategies of Dealing with an Intercurrent Event

- 1. Treatment policy
- 2. Composite
- 3. Hypothetical
- 4. Principal stratum
- 5. While on treatment

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Major Depressive Disorder (MDD): Types of Studies

- Monotherapy treatment:
  - Placebo control
  - Active control
- Adjunctive treatment

Studies: Short-term response (ST) or Long-term maintenance (LT)

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MDD: Intercurrent Events (IE)

- Treatment discontinuation
- Treatment non-compliance (intermittent or partial treatment adherence)
- Protocol allowed dose adjustment
- Initiation of rescue therapy (or intermittent rescue therapy)
- Initiation or adjustment of concomitant medication related to other symptoms related to depression (e.g. for insomnia)
- Any other major protocol deviations that could influence depression scores (i.e. dose adjustments of the study drug not allowed by the protocol or initiation of concomitant medication not allowed by the protocol)
- Discontinuation of the background medication – adjunctive trials only
- Study discontinuation
- Intermediate events (e.g. missed visits, missed data collections) leading to intermediate missing for the variable

Note: Each IE could be considered as a unified event or could be further divided into sub-categories (e.g. treatment discontinuation by reason)

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Example: Estimand 1
Monotherapy, Pbo Controlled ST Phase 2 Trial

- Trial Objective: The drug has superior benefit in treating MDD vs placebo
- Stakeholder: Sponsor
- Estimand Scientific Question of Interest: What is the effect of the drug when taken as intended in the protocol?
- Estimand Utility: “Eliminate” the effects of the intercurrent events considered confounding to the scientific question of interest by envisaging a hypothetical scenario for the subjects’ clinical course after these intercurrent events.

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Estimand 1 Components

- Population: Subjects with MDD acute episodes, as defined by the inclusion-exclusion criteria of the study
- Variable: Change from baseline to Week X (e.g. Week 6) in a depression measure (e.g. HAMD, MADRS)
- Intercurrent events and their corresponding strategies: *see next slide*
- Summary measure: Difference in variable treatment means

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Estimand 1 Strategies for Intercurrent Events

Intercurrent Events	Name of Strategy for Addressing Intercurrent Events and Its Description
Treatment Discontinuation	Hypothetical "as own treatment group" strategy: Clinical course is the same as other subjects in the same treatment group, who had not discontinued study treatment.
Modest Treatment Non-compliance	Treatment Policy strategy: All observed values of the variable are used, regardless of whether or not the subject had experienced the intercurrent event.
Severe Treatment Non-compliance	Hypothetical "as own treatment group" strategy
Protocol allowed dose adjustment (if applicable)	Treatment Policy strategy
Initiation of rescue therapy, expected to have direct effect on depression scores (if applicable)	Hypothetical "as own treatment group" strategy
Initiation or adjustment of concomitant medication related to other symptoms related to depression with direct effect on depression scores(specify these medications)	Hypothetical "as own treatment group" strategy
Initiation or adjustment of concomitant medication related to other symptoms related to depression with NO direct effect on depression scores	Treatment Policy strategy
Any other major protocol deviations that could influence depression scores (i.e. dose adjustments of the study drug not allowed by the protocol or initiation of concomitant medication not allowed by the protocol)	Hypothetical "as own treatment group" strategy
Study Discontinuation	Strategy covered by the treatment discontinuation strategy
Intermediate events leading to intermediate missing for the variable	Hypothetical "as own treatment group" strategy

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Discuss Next Steps after Estimand 1 Selection

- Trial Design
- Estimator:
  - Main
  - Sensitivity

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Example: Estimand 2
Adjunctive, Placebo Controlled ST Phase 3 Trial

- Trial Objective: The drug has superior benefit in treating MDD vs placebo, when administered with the protocol allowed background medication
- Stakeholder: Regulatory
- Estimand Scientific Question of Interest: What is the effect of assigning subjects to the experimental add-on drug administered together ONLY with the protocol allowed background medication?
- Estimand Utility: The estimand with the most broadly use of the observed data, "eliminating" the effects of any background medications not allowed by the protocol

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Estimand 2 Components (Same as Estimand 1)

- Population: Subjects with MDD acute episodes, as defined by the inclusion-exclusion criteria of the study
- Variable: Change from baseline to Week X (e.g. Week 6) in a depression measure (e.g. HAMD, MADRS)
- Intercurrent events and their corresponding strategies: *see next slide*
- Summary measure: Difference in variable treatment means

Estimand 2 Strategies for Intercurrent Events

Intercurrent Events	Name of Strategy for Addressing Intercurrent Events and Its Description
Discontinuation of the Add-on Treatment	Treatment Policy strategy: All observed values of the variable are used, regardless of whether or not the subject had experienced the intercurrent event.
Discontinuation of the Background Treatment	Hypothetical "as reference group" strategy: Clinical course is based on that of a reference group (e.g. placebo + background group), as if, after discontinuation the subject had always been member of the reference group.
Add-on or Background Treatment Non-compliance	Treatment Policy strategy
Protocol allowed dose adjustment (if applicable)	Treatment Policy strategy
Initiation of rescue therapy (if applicable)	Treatment Policy strategy
Initiation or adjustment of concomitant medication related to other symptoms related to depression	Treatment Policy strategy
Initiation of concomitant medication not allowed by the protocol	Same hypothetical strategy as for Discontinuation of the Background Treatment
Study Discontinuation	Same hypothetical strategy as for Discontinuation of the Background Treatment
Intermediate events leading to intermediate missing for the variable	Hypothetical "as own treatment group" strategy

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Discuss Next Steps after Estimand 2 Selection

- Trial Design
- Estimator:
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  - Sensitivity

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Wrap-Up

- Summary of discussion points
- Any other items?