ICH E9(R1) estimand framework & CDISC

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12 May 2023

Estimands session at IX CDISC Italian User Network

All expressed views belong to the author and cannot be associated with the views of CBG-MEB, EMA, Biogen or any of the working groups where I have membership.
ICH E9(R1) Timeline

• 2010 US National Research Council report on missing data (& estimands)
• E9(R1) Expert Working Group
  • Oct 2014 Concept Paper
  • August 2017 Step 2b
  • December 2019 final version step 5
ADDENDUM ON ESTIMANDS AND SENSITIVITY ANALYSIS IN CLINICAL TRIALS TO THE GUIDELINE ON STATISTICAL PRINCIPLES FOR CLINICAL TRIALS

E9(R1)

Final version
Adopted on 20 November 2019

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of ICH regions.
Estimands in literature
Estimands in Regulatory guidance?

8.1.2. Target of estimation in the prodromal AD /MCI due to AD Preclinical AD setting

In the prodromal/MCI setting, patients are not from the beginning of the trial on a stable background therapy. The initiation of a non-investigational symptomatic treatment as an interventional event that will influence the measurement of the outcome variable should be addressed in the estimand. As above, the treatment effect if symptomatic medication that has been introduced could be an appropriate target of estimation, providing that reliable estimation can be identified. An alternative strategy might be to integrate the event (e.g., to define a non-responder as a patient with a certain degree of progression on additional symptomatic medication).

Guideline on the clinical investigation of medicines for the treatment of Alzheimer’s disease CPMP/EWP/553/95 Rev.2

The war in Ukraine may impact ongoing clinical trials in aspects that are shared with the COVID-19 pandemic. In this regard, Sponsors are encouraged to consult the EMA (Points to consider on modifications of clinical trials COVID-19 on methodological aspects of ongoing trials – Revision J) and take into consideration other relevant points discussed there that are also applicable in this context. Likewise, it is recommended to seek Scientific Advice early in the process if substantial modifications to the current protocol and/or analysis plan are considered necessary. These aspects related to the impact of the war on trial design elements, recruitment, data collection, analysis and interpretation of results will be thoroughly reflected upon during requests for EMA Scientific Advice and assessment of affected clinical trial data submitted to the EMA for Marketing Authorisation Application.
Estimands initiatives in pharma industry?
The ICH E9(R1) estimands framework

• “This addendum presents a structured framework to strengthen the dialogue between disciplines involved in the formulation of clinical trial objectives, design, conduct, analysis and interpretation, as well as between sponsor and regulator regarding the treatment effect(s) of interest that a clinical trial should address.”
The estimand definition

Estimand:
A precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarises at a population-level what the outcomes would be in the same patients under different treatment conditions being compared.
The intercurrent event definition

**Intercurrent Events:**
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.
Missing data definition

Missing Data:
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.
Estimand attributes
Strategies for intercurrent events

- Treatment policy strategy
- Hypothetical strategy
- Composite variable strategies
- While on treatment strategies
- Principal stratum strategies
Strategies for intercurrent events

• Treatment policy strategy

(Actively!) Ignore the intercurrent event

- it requires complete subject follow-up
Patient journeys in a trial (TP)
Strategies for intercurrent events

• Hypothetical strategy

Envisage a scenario where the intercurrent event would not occur
Patient journeys in a trial (Hyp)

Randomisation

Timeline

Primary endpoint

COVID19 pandemic

Patient decessoed

Lost to follow-up

Add-on medication

Start of rescue medication

Treatment completion

Treatment discontinuation

Patient deceased

Patient 1

Patient 2

Patient 3

Patient 4

Patient 5

Patient 6

Patient 7
Strategies for intercurrent events

• Composite variable strategies
Consider the intercurrent event as part of the variable.
Could be an event or could be a certain value if scores are used.
Patient journeys in a trial (Comp)
Strategies for intercurrent events

• While on treatment strategies
Interest is in the patient’s trajectory prior to the intercurrent event.
Use only outcome values before the intercurrent event.
Patient journeys in a trial (WoT)

Timeline

Randomisation

Primary endpoint

Start of rescue medication

Patient deceased

Lost to follow-up

Add-on medication

COVID19 pandemic

Treatment discontinuation

Treatment completion

Patient 1

Patient 2

Patient 3

Patient 4

Patient 5

Patient 6

Patient 7

COVID19 pandemic

Patient deceased

Start of rescue medication

Add-on medication

Patient deceased

Lost to follow-up
Strategies for intercurrent events

• Principal stratum strategies

Interest is in a certain subpopulation that would/would not experience a certain intercurrent event of interest

=! subgroup/PP...
Patient journeys in a trial (PS)
What do ICH E9(R1) and CDISC have in common?

- Nothing and a lot, at the same time
phuse working group with multiple subteams

Implementation of Estimands (ICH E9 (R1)) using Data Standards

Created by, last modified by Lauren Shinaberry on May 03, 2023

Optimizing the Use of Data Standards

Project Scope

Impact assessment of the estimands framework and recommendations/best practices (where applicable) for implementing the framework in the following areas:

- Data Collect Design/CDASH
- SDTM
- ADAM (including handling of intercurrent events, missing data imputation) – Analysis Displays
- CDISC and ADAG

Development of new standards is not in scope, and any impact findings that may necessitate new standard development will be shared with CDISC for their consideration. Examples may be created on how to implement the framework by using permitted extensions to the existing data standards.

Project Leads

<table>
<thead>
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<th>Name</th>
<th>Email</th>
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<tbody>
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Objectives & Deliverables

Submit abstracts for multiple conferences
Develop draft White Paper for internal project review prior to PHUSE Working Group Review and Public Review

Timelines

Q2 2023
Q3 2023

Project Members

<table>
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<tr>
<th>Name</th>
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<td>Munish Mahra</td>
<td>Tigramed</td>
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Describe the study objective in terms of the estimands framework (**WHAT**).

Statistical details on estimand (**WHAT detailed**), link estimands to their estimators (**HOW performed statistically**).

HOW the relevant aspects of estimands were **implemented** in the data. New section on estimands in CSDRG & ADRG.

Dedicated datasets and variables to document the traceability of estimands and impact in the data.
Data Collection & Tabulation
Need for Data Collection Enhancements

- Accurate collection of intercurrent events is critical in defining estimands and constructing the estimators.
- Granular data collection of the reasons for treatment discontinuations (e.g., AE, LoE, condition improved, AE & LoE etc...).

Data collection enhancements enable to use the prespecified strategies to handle intercurrent events based on the underlying reasons.
Commonly Observed Intercurrent Events

Direct Consequences of Treatment

➢ Treatment Discontinuation
➢ Treatment Interruption
➢ Infusion Interruption
➢ Dose Adjustment
➢ Treatment Delay

Additional / Alternative Treatment

➢ Concomitant Medication
➢ Concomitant Procedure
➢ Subsequent Cancer Surgery*
➢ Subsequent Radiotherapy*

*oncology
Data Collection & Tabulation - Summary

Data Collection
- Accuracy and Granularity
- Sponsors should assess study designs

Codelist
- Proposal submitted to CDASH/CDISC
- Recommendations for new terms

SDTM
- Estimands framework has no impact
- Follow SDTM IG & Conformance Rules

cSDRG
- Section for Intercurrent Events
- Define, collection and mapping
Data Analysis
Estimands Impact on Analysis

Mapping intercurrent events
- Identifying subjects and data points for estimand-based analyses
- Enhanced ADaM dataset guidance is needed

Documentation
- Estimands description and implementation

Based on user needs
- Proposed examples will be offered in white paper
NEW Intercurrent Events Dataset (ADICE)

- Documents intercurrent events across all estimands
- Facilitates traceability and inclusion of intercurrent events into other datasets
- OCCDS structure (one record per intercurrent event)
- This is an optional and supportive dataset to consolidate all intercurrent events in one place

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<th>ASEQ</th>
<th>ATERM</th>
<th>ADECOD</th>
<th>ASTDT(M)</th>
<th>AENDT(M)</th>
<th>SRCDOM</th>
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- Optional columns per estimand:
  - **ESTzzSTR**: Strategy (e.g., treatment policy) for handling the intercurrent event for estimand zz
  - **ESzzGRID**: Group multiple intercurrent events affecting a datapoint for estimand zz
NEW ADaM Dataset Variables

- ADSL (Subject-Level)
  - **ESTzzFL**: Subjects considered in all estimand zz estimations

- BDS (Basic Data Structure)
  - **ESTzzRFL**: Record-level datapoints considered in all estimand zz estimations
  - **ICESEQzz**: Links the intercurrent event(s) impacting the datapoint for estimand zz
    - Point to **ASEQ** of the single intercurrent event affecting the datapoint
    - Point to **ESzzGRID** of the multiple intercurrent events affecting the datapoint (advanced)
  
  Note: if ADICE is not implemented: **ICEDOMzz** and **ICEVARzz** link to SDTM source

- Similar for OCCDS and ADaM OTHER structures
Data Analysis - Summary

ADICE
- Consistent documentation of all intercurrent events
- Support harmonized workflows

New ADaM Variables
- ADSL: New estimand analysis set flag
- BDS: New record level data point flag and intercurrent event traceability variables

Guidance
- Building upon existing ADaM-IG that already addresses analysis features (estimations).

‘Data analysis’ becomes more complex & granular – ‘Data derivation’ + ‘Estimation’
Conclusion & Next Steps
Conclusion – E9(R1) & CDISC

- Cross-functional interaction critical
- Impacts protocol, data collection and data analysis
- Different implementation approaches may be appropriate
- Need to update/extend existing data standards
- Consistent implementation of estimands is beneficial
Thank you!


8. https://advance.phuse.global/display/WEL/Implementation+of+Estimands+%28ICH+E9+%28R1%29%29+using+Data+Standards
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