18th Annual Scientific Meeting

Estimands and Missing Data Working Group

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Outline

- Objectives and progress of this working group (ISCTM Estimand WG)
- Brief Background:
    - ICH E9(R1) Addendum
    - ICH E9(R1) – Recommended Trial Planning Framework
    - Attributes of an estimand
- Discussion

Objectives and Progress of ISCTM Estimand WG

- 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.
- Progress on manuscript development:
    - First draft developed by a core team; multiple estimand examples developed for MDD
    - To be reviewed by a larger team when finalized
    - Target timeline to finalize manuscript: Q2-3 2022

ICH E9(R1) Addendum - Background

- Final ICH E9(R1) Addendum on “Estimands and Sensitivity Analysis in Clinical Trials” released in Nov 2019: https://database.ich.org/sites/default/files/E9-R1_Step4_Guideline_2019_1203.pdf
- Increasing Pharma-regulatory interactions and requests seen on this topic

E9(R1) EWG Addendum: Statistical Principles for Clinical Trials

The Addendum provides clarification on E9 and an update on the choice of estimand in clinical trials to describe an agreed framework for planning, conducting and interpreting sensitivity analyses of clinical trial data. This Addendum focuses on statistical principles related to estimands and sensitivity analysis, not on the use or acceptability of specific statistical procedures or methods. The primary focus of the Addendum is on confirmatory clinical trials.

Date of *Step 4*: 20 November 2019

Guideline

E9(R1) Addendum

Endorsed Documents

E9(R1) Concept Paper

WG Presentations / Trainings

E9R1 EWG Step 4 Training Material ZIP

E9R1 EWG Step 4 Training Material PDF

Status: *Step 5*

Implementation status:

ANVISA, Brazil - Not yet implemented; Date: 1 December 2023; Reference: N/A

EC, Europe - Implemented; Date: 30 July 2020; Reference: EMA/CHMP/ICH/436221/2017

FDA, United States - Implemented; Date: 11 May 2021; Reference: Posted on FDA, United States website

HSA, Singapore - In the process of implementation;

Health Canada, Canada - Implemented; Date: 21 July 2020; Reference: File #: 20-109237-45

MFDS, Republic of Korea - In the process of implementation; Date: 1 November 2021;

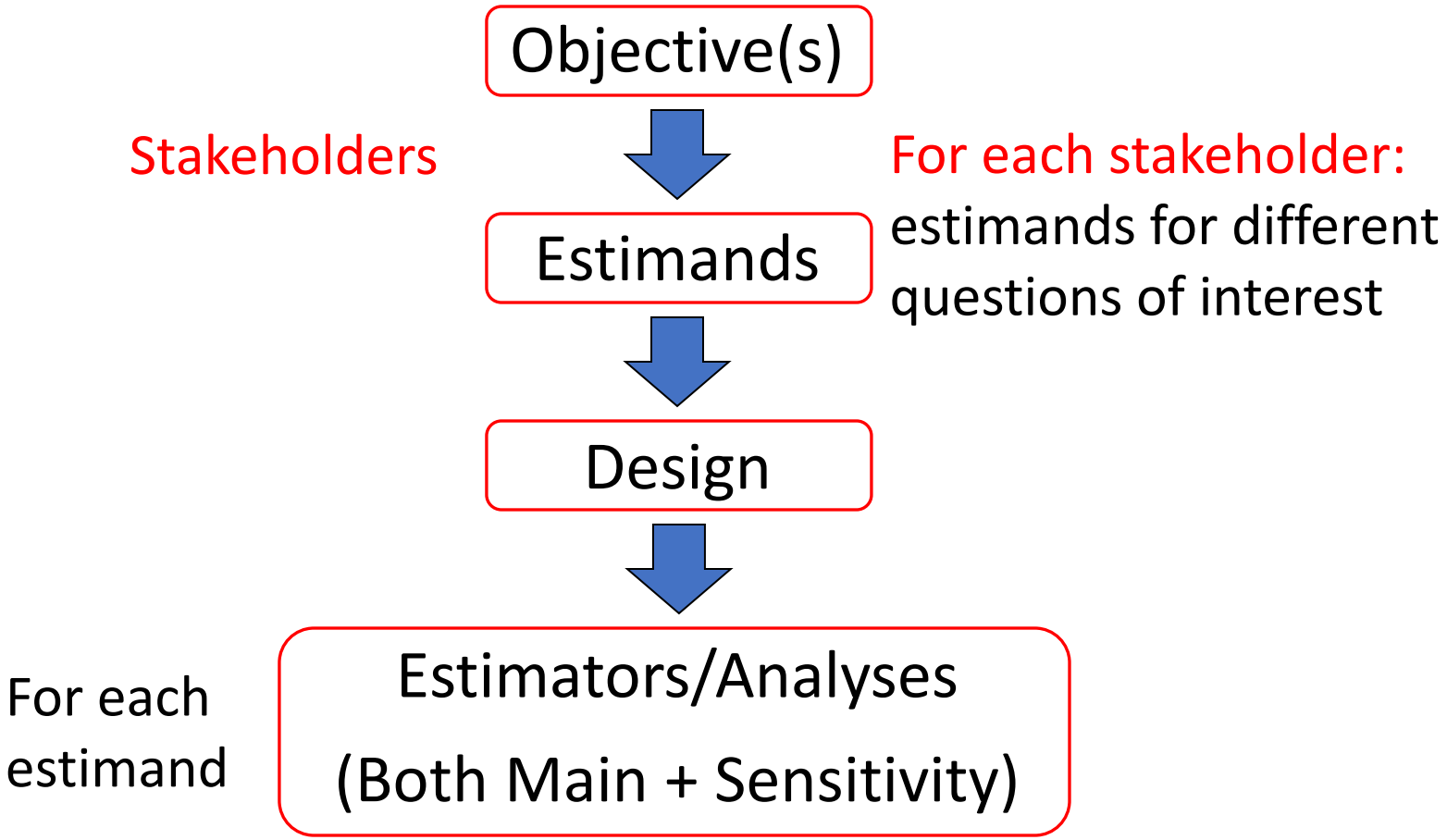
MHLW/PMDA, Japan - In the process of implementation;

NMPA, China - In the process of implementation; Date: 25 January 2022; Reference: NMPA, China Announcement No. 16 [2021

Swissmedic, Switzerland - Implemented; Date: 30 November 2019;

TFDA, Chinese Taipei - Implemented; Date: 9 February 2021; Reference: Updated-Announcement for ICH Guidelines Recognition List

ICH E9(R1) - Trial Planning Framework



Estimand - Five Attributes

An estimand is a precise description of the treatment effect reflecting the clinical question posed by a given clinical trial objective.

Who to study

Endpoint for an individual

Mean difference, proportion difference, hazard ratio

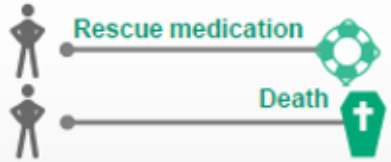
Population

Variable

Population-level summary

Treatments being compared

The description of an estimand will not be complete without reflecting how potential **intercurrent events** are addressed in the scientific question of interest.



Might include individual contributing factors, incl. combinations thereof: e.g. active drug / placebo, background medication, rescue medication

Why 5 attributes in an estimand?

Estimand 1 – the Confounded / Reality Recipe!

What is the difference between means in

change from baseline HbA1c after 26 weeks

in patients with Type 2 diabetes,

treated with
oral semaglutide 14 mg versus placebo*,
irrespective of adherence to IMP and with
use of rescue medication as required?

*(as an adjunct to diet and exercise);
IMP = investigational medicinal product

Population-level summary measure

Endpoint

Population

Treatment Conditions

Strategies for Intercurrent Events

Slide 24

ICH E9(R1) Identified Strategies of Addressing an Intercurrent Event (ICE)

- Treatment policy
- Composite
- Hypothetical
- Principal stratum
- While on treatment

Potential Discussion Topics

- Documenting estimands in protocols and SAPs for primary and major secondary endpoints
- Estimands for different stakeholders in a single trial
- Trial objective(s) versus questions of interest
- How to define questions of interest – connection with strategies used for intercurrent events
- What types of questions can a randomized withdrawal trial answer?
- Applications for Principal Stratum strategy
- Steps from estimand to estimator
- Main vs sensitivity vs supplementary analyses

Back-Up

A thinking process…

1. Therapeutic setting and intent of treatment determining a trial objective
2. Identify intercurrent events
3. Discuss strategies to address intercurrent events
4. Construct the estimand(s)
5. Align choices on trial design, data collection and method of estimation
6. Identify assumptions for the main analysis and suitable sensitivity analyses to investigate these assumptions
7. Document the chosen estimands

Process - Estimand Definition

- Identify the stakeholder for whom the estimand is being defined
- Define:
  - Decision that the stakeholder needs to make
  - Overall trial objective
  - Clinical question of interest in line with the objective
  - Utility of this question to stakeholder
- Identify the applicable intercurrent events (ICEs)
- Define the five attributes of the estimand aligned with the question of interest