17th Annual Scientific Meeting

Estimands and Missing Data Working Group

Chairs:
Elena Polverejan, PhD
Pilar Lim, PhD

Outline

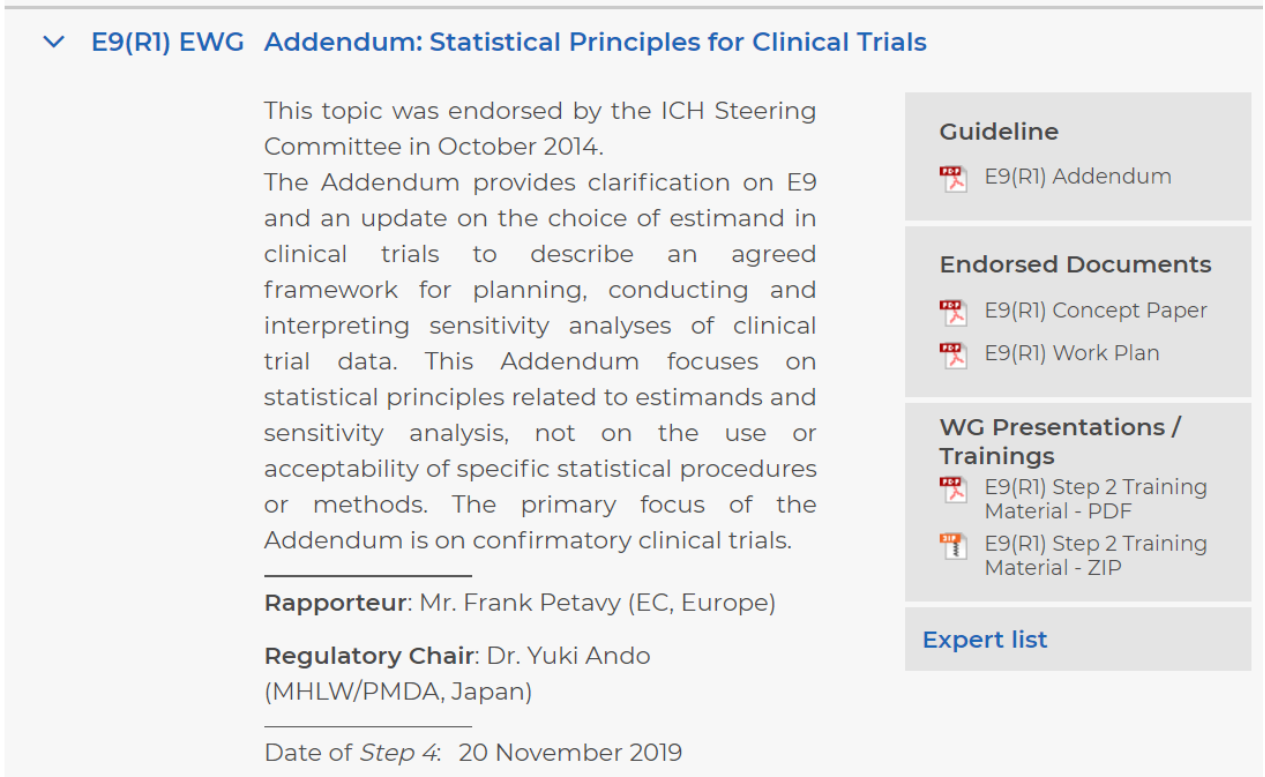
- Objectives and progress of this working group (ISCTM Estimand WG)
- Background:
    - ICH E9(R1) Addendum
    - ICH E9(R1) – Recommended Trial Planning Framework
    - Attributes of an estimand
    - Process – estimand definition
- Example from Major Depressive Disorder (MDD)
- Potential Discussion Topics

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 for an MDD indication to be included
    - To be reviewed by the larger team when finalized
    - Target timeline to finalize manuscript: Aug 2021

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

This topic was endorsed by the ICH Steering Committee in October 2014.
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.

Rapporteur: Mr. Frank Petavy (EC, Europe)

Regulatory Chair: Dr. Yuki Ando (MHLW/PMDA, Japan)

Date of *Step 4*: 20 November 2019

Guideline
E9(R1) Addendum

Endorsed Documents
E9(R1) Concept Paper
E9(R1) Work Plan

WG Presentations / Trainings
E9(R1) Step 2 Training Material - PDF
E9(R1) Step 2 Training Material - ZIP

Expert list

Status: *Step 5*

Implementation status:

ANVISA, Brazil - Not yet implemented; Reference: N/A

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

FDA, United States - In the process of implementation;

HSA, Singapore - In the process of implementation;

Health Canada, Canada - Implemented; Date: 21 July 2020;

MFDS, Republic of Korea - Not yet implemented; Date: 1 January 2021;

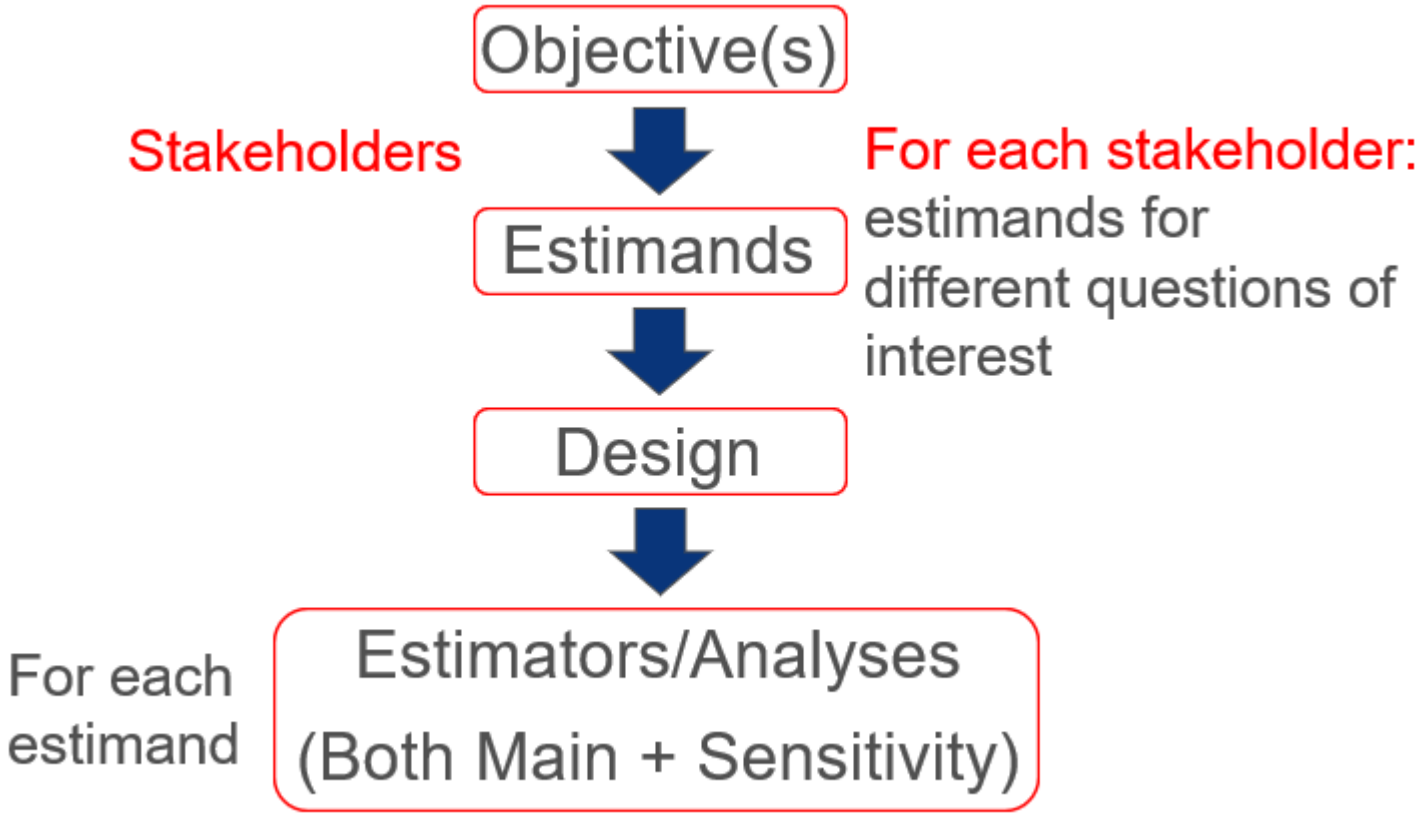
MHLW/PMDA, Japan - In the process of implementation;

NMPA, China - In the process of implementation;

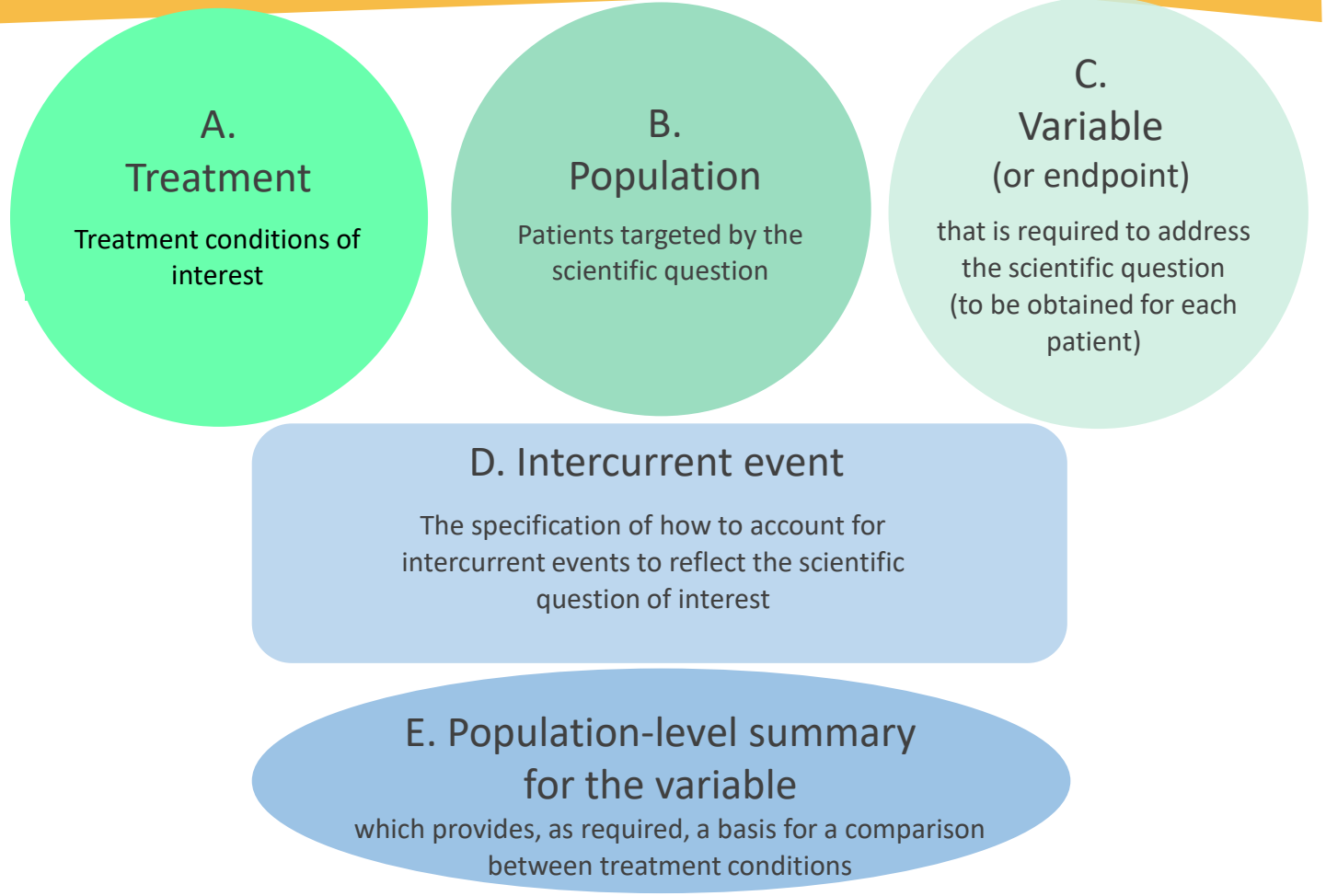
Swissmedic, Switzerland - Implemented; Date: 30 November 2019;

TFDA, Chinese Taipei - In the process of implementation;

ICH E9(R1) - Trial Planning Framework



Slide from ICH E9 (R1) EWG



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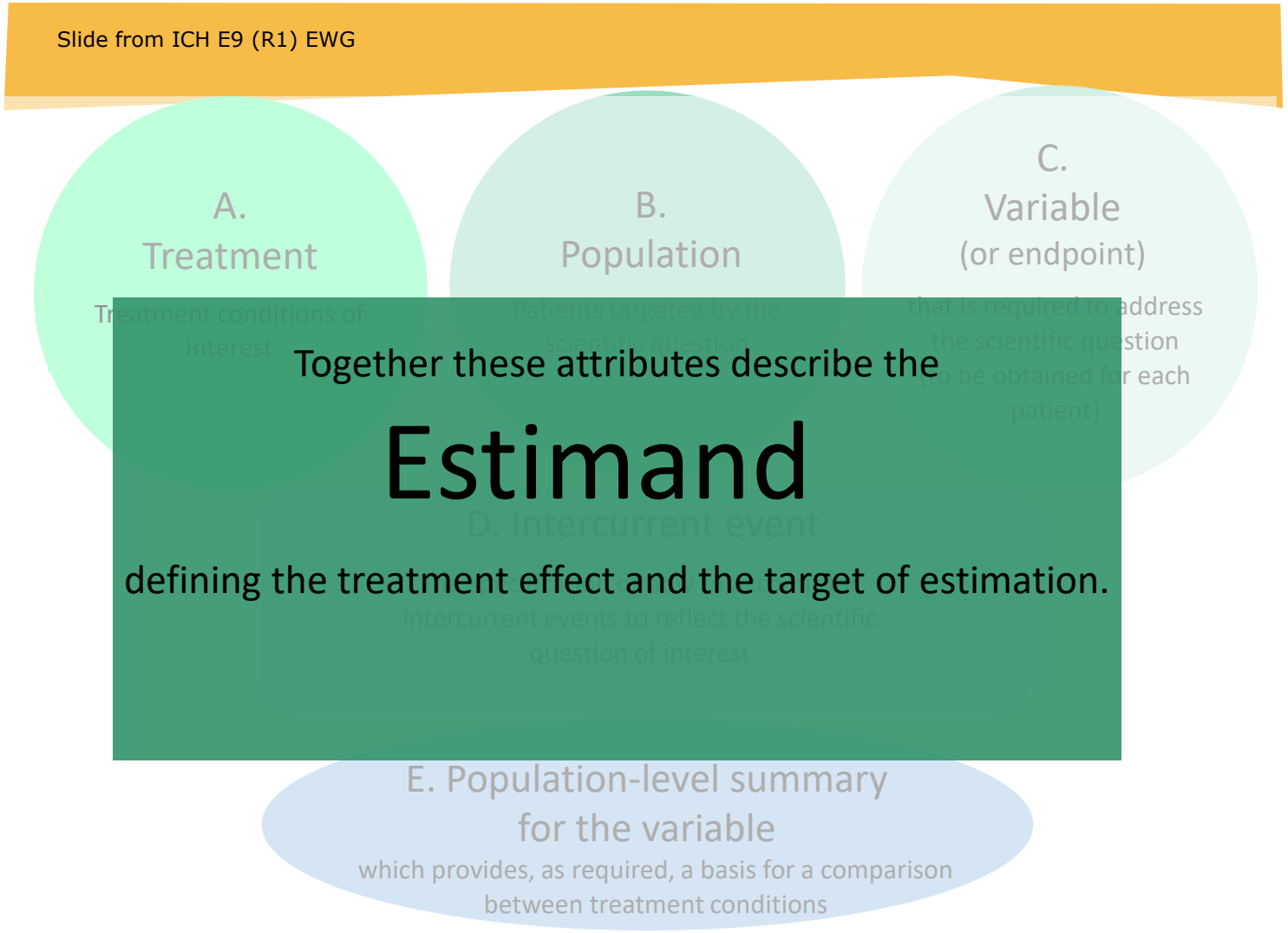

ICH E9(R1) Identified Strategies of Addressing an Intercurrent Event (ICE)

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

Process - Estimand Definition

- Identify the stakeholder for whom the estimand is being defined
- Define:
  - Clinical question of interest that the estimand addresses
  - Decision that the stakeholder needs to make (superiority, non-inferiority, Go/No Go, identify dose response etc.)
  - Utility of the estimand to stakeholder (i.e. how the estimand addresses the needs of the stakeholder).
- Identify the applicable intercurrent events (ICEs)
- Define the five attributes of the estimand

Example MDD

Set-up: monotherapy, placebo-controlled short-term trial in MDD

- Stakeholder: Health Authority Agency
- Question of Interest: What is the effect of assigning patients to the investigational medicine X vs placebo, regardless of discontinuation and in absence of other pharmacological treatments?
- Decision: Determine superiority of the investigational medicine X vs placebo
- Utility of the estimand to stakeholder: The estimand with the most broadly use of the observed data, “eliminating” the effects of any other pharmacological treatments than investigational medicine X

Estimand Definition

- **Treatment condition of interest:** Assignment to investigational medicine X at the dose and frequency of administration detailed in the protocol, regardless of discontinuation and in absence of other pharmacological treatments for MDD;
- **Alternative treatment condition:** Assignment to Placebo, regardless of discontinuation and in absence of other pharmacological treatments for MDD;
- **Population:** Subjects with a diagnosis of MDD and fulfilling all other eligibility criteria as per protocol;
- **Variable:** Change from baseline to Week 8 in the total score of the 17-items version of the HDRS;
- **Population-level summary:** Difference in treatment means;
- **Intercurrent events and Corresponding Strategies:** see next slide

Estimand Definition (Cont.)

- **Intercurrent events and Corresponding Strategies:**

Event	Strategy	Description*
Treatment discontinuation	Treatment-policy, as reflected in the Treatment definition	Values are of relevance regardless of the occurrence of this ICE
Starting other pharmacological treatments for MDD	Hypothetical, as reflected in the Treatment definition	A scenario is envisaged in which other treatments are not available

* Description of a strategy can be omitted from this table if that strategy is already incorporated into another attribute, as in this example.

Potential Discussion Topics

- ICEs vs events leading to missing data (e.g. study withdrawal)
- COVID-19 pandemic impact: estimands and estimators
- Steps from estimand to estimator
- Sensitivity analyses: Changing assumptions for model vs data not used in the analysis vs missing data
- Supplementary analyses
- Documenting estimands in protocols and SAPs for primary and major secondary endpoints
- Estimands for different stakeholders in a single trial