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Estimands in Diabetes Clinical Trials

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Conflict of Interest

- No competing interest

Outlines

- Background: Before Estimands
- What is Estimand?
- Estimands in Diabetes Trials

Background: Before Estimands

- Intention-to-treat (ITT) analysis
- Last-observation-carried-forward
- Example: Dapagliflozin initial application to FDA in 2011

Intention-To-Treat (ITT) Analysis

- ITT: all randomised participants are included in the final analysis regardless of the occurrence of intercurrent events
- Mirrors real-life clinical practice
- ITT also known as “Full analysis set”
- Analyse as randomized, not as treated

https://database.ich.org/sites/default/files/E9_Guideline.pdf

Intention-To-Treat (ITT) Analysis

- Prevent the conscious or unconscious attempts to influence the results of the study by excluding the patients
- Conservative for estimates of the treatment difference
- Might underestimate treatment effect

Intercurrent events

- Intercurrent events occur post-randomisation
- Trial protocols often not explicitly mention methods of handling intercurrent events

- Examples include
  - Use of rescue medication
  - Premature discontinuation of trial medication
  - Loss to follow-up
  - Death

- Some intercurrent events might lead to no observed values at the end of trial

Last-observation-carried-forward (LOCF)

- Last observed value before the intercurrent events (rescue medication, premature discontinuation, loss to follow-up) is carried forward as the end-of-trial value

- Deficiencies of LOCF method
  - Overestimation: it assumes that patients who have a good short-term outcome will continue to have a good outcome going forwards

  - Under-estimation of the treatment effect which appears late in the trial

Example: Dapagliflozin application to FDA (2011)

- Astra-Zeneca and Bristol-Myers Squibb submitted efficacy data of Dapagliflozin for treatment of type 2 diabetes
- Dapagliflozin: first sodium glucose co-transporter-2 inhibitor
- Primary end point: Change in HbA1c from baseline at 24 weeks
- Rescue medications allowed according to pre-specified glucose threshold

Example: Dapagliflozin application to FDA (2011)

- Statistical analysis included all randomised patients
  - Who received at least one dose and
  - Who had baseline HbA1c value and at least one-post baseline value

- HbA1c observed values after rescue medications were set to missing

- Last pre-rescue medication values were carried forward as the end-of-trial values

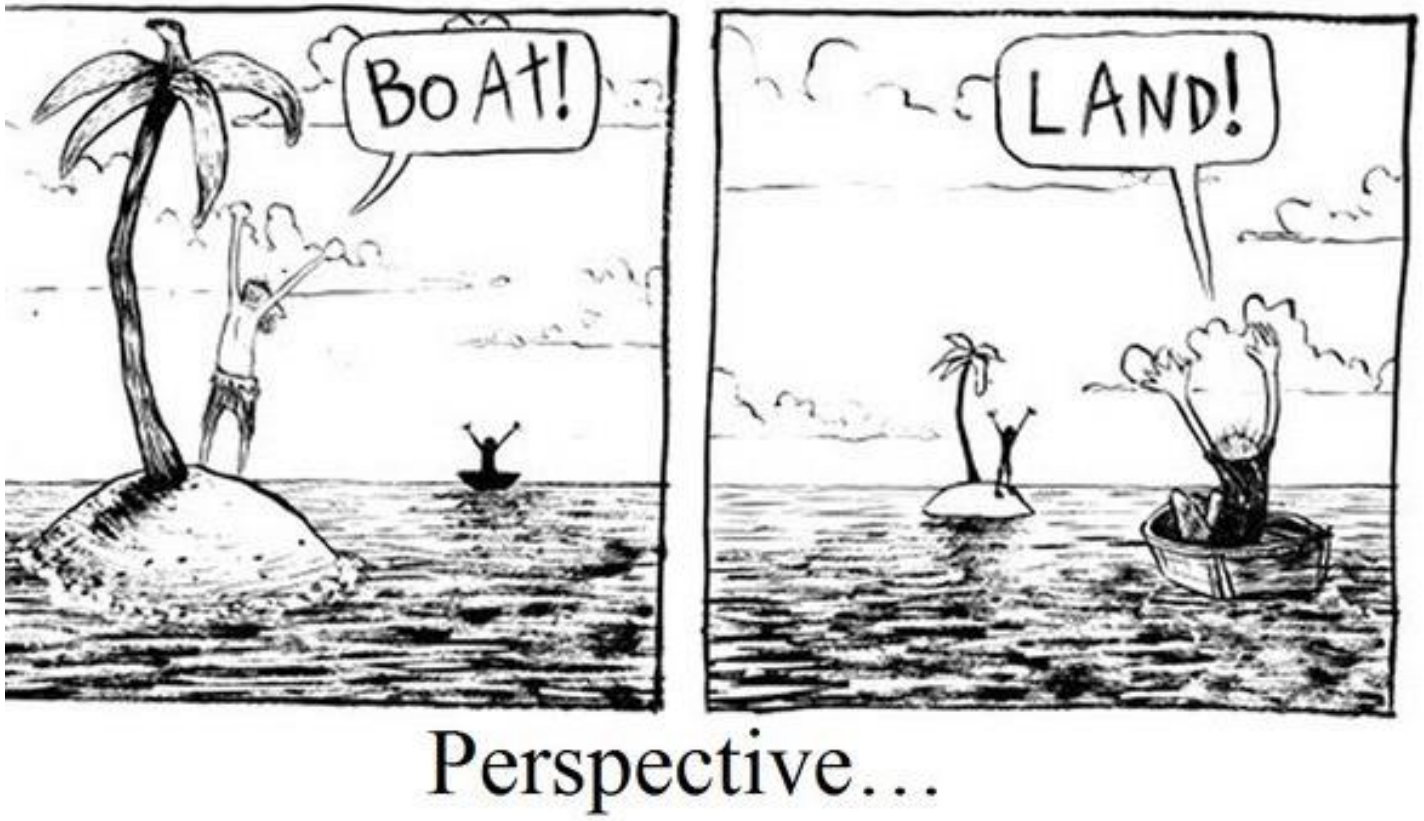
Example: Dapagliflozin application to FDA (2011)

- FDA reviewer
  - “more awareness in the statistical community of the limitations of LOCF”
  - “my own preferred analysis simply uses the observed values of patients who were rescued.”

- Sponsors’ perspective: To establish the treatment effect of Dapagliflozin had no patient received rescue medication

- FDA’s perspective: To establish treatment policies ‘Dapagliflozin plus rescue’ versus ‘Control plus rescue’

Different stakeholders-- Different perspectives



What is Estimand?

- Definition
- Attributes of Estimand in context with Diabetes trial
- Estimand strategies

Estimand

- A detailed description of what needs to be estimated to address scientific question of interest

- ICH E9 (R1) presented ‘Estimand Frame Work in Clinical Trial’
  - Endorsed by the ICH Assembly, released for public consultation- August 2017
  - Adopted by the Regulatory Members of the ICH Assembly- November 2019

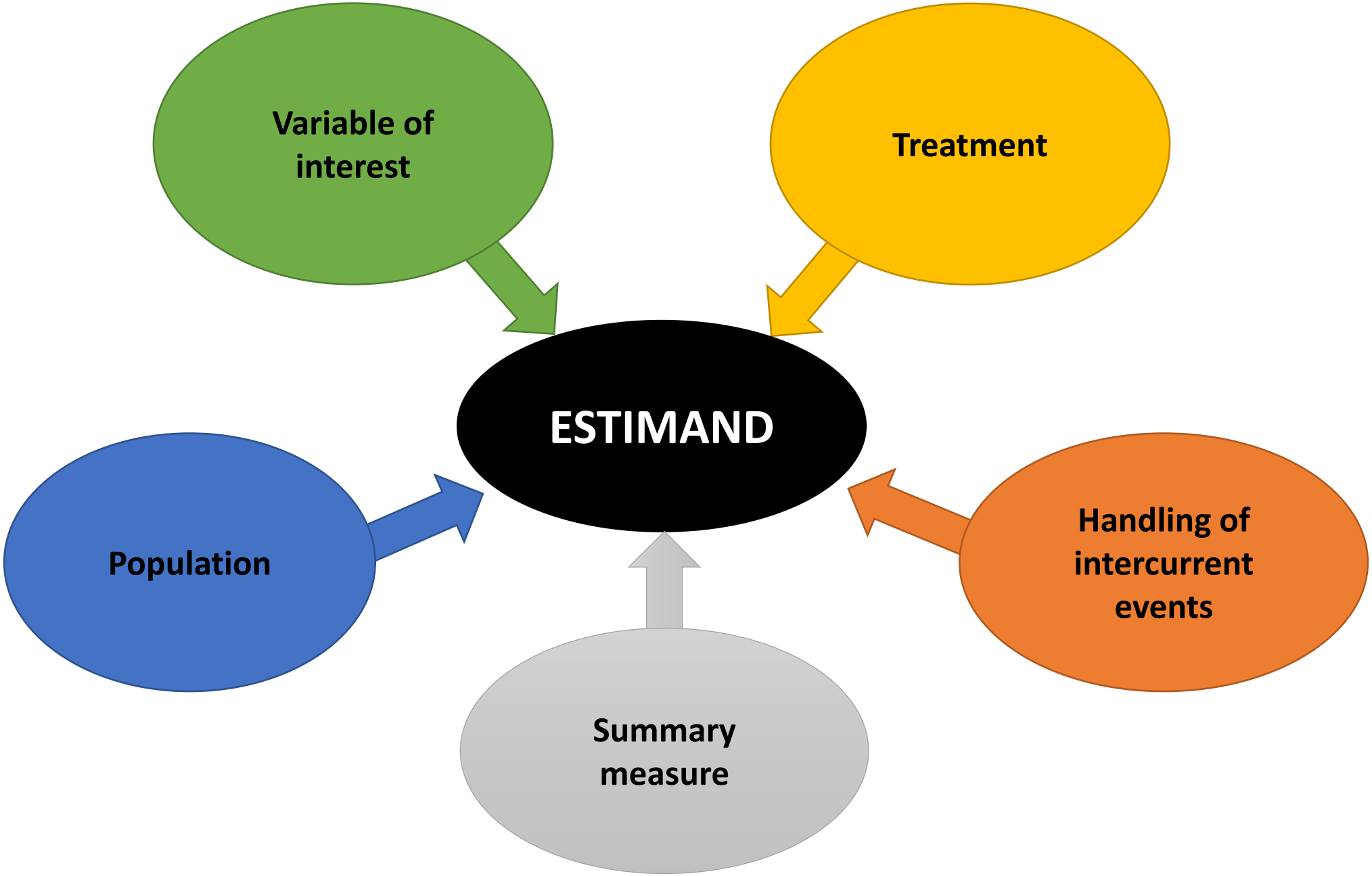
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 February 2020
EMA/CHMP/ICH/436221/2017
Committee for Medicinal Products for Human Use

ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials

Step 5

Transmission to CHMP	July 2017
Adoption by CHMP for release for consultation	20 July 2017
Start of consultation	31 August 2017
End of consultation (deadline for comments)	28 February 2018
Final adoption by CHMP	30 January 2020
Date for coming into effect	30 July 2020


Variable of interest
Treatment
ESTIMAND
Population
Handling of intercurrent events
Summary measure

Estimand Strategies

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

Estimand strategies

1. Treatment policy strategy
   - Observed values of a variable are used regardless of intercurrent events
   - Broadly correspond to ITT analysis

2. Hypothetical strategy
   - A scenario is envisaged in which the intercurrent event would not occur
   - A wide variety of hypothetical scenarios can be envisaged, but some likely to be of more clinical or regulatory interest than others
   - Should be made clear what hypothetical scenario is envisaged

Estimand strategies

3. Composite strategy
   - The intercurrent event is integrated with one or more measures of clinical outcome as a combined variable of interest
   - Terminal events, such as death, are perhaps the most salient examples of the need for the composite strategy

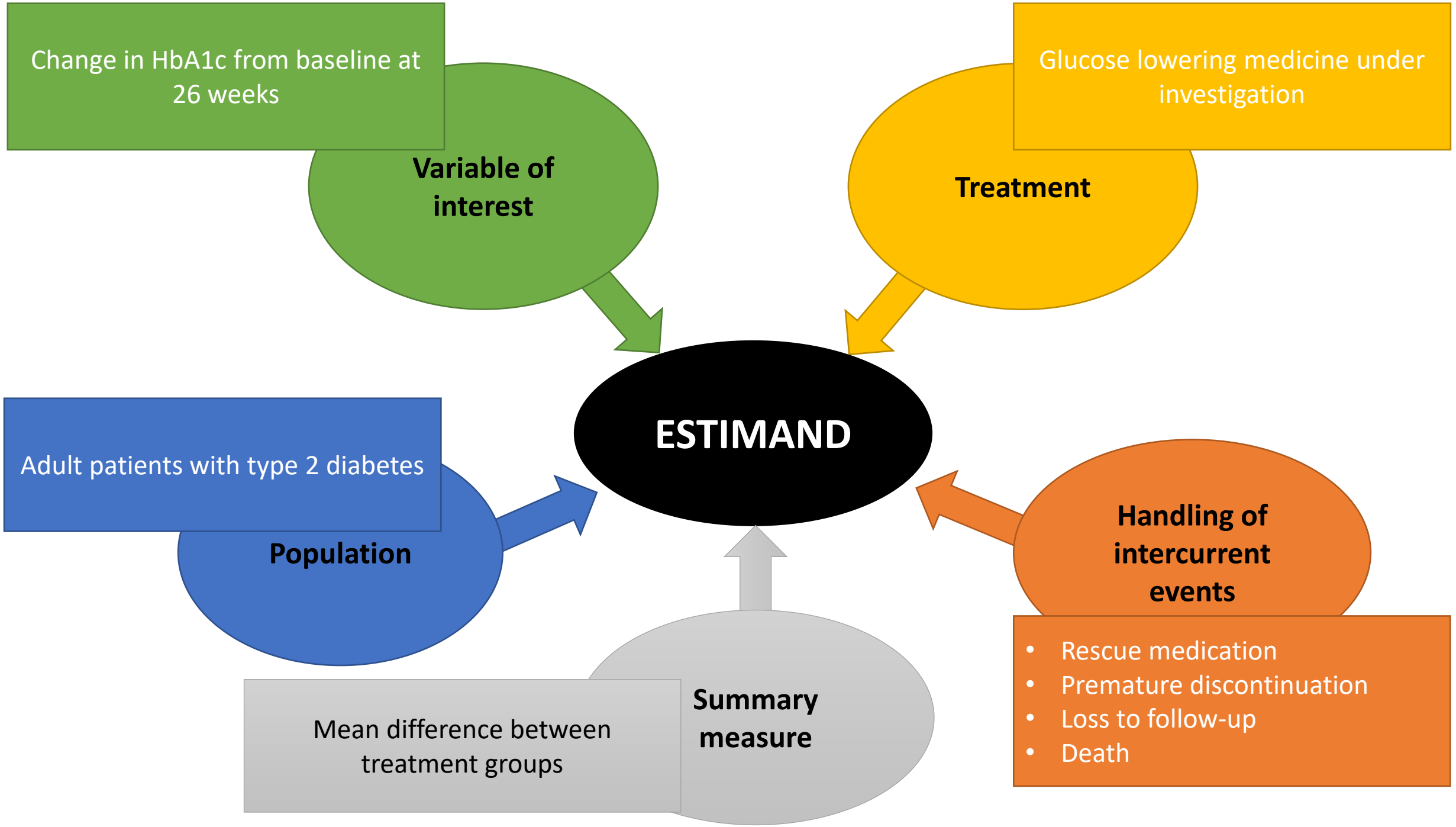
4. Principal stratum strategy
   - Includes subset of trial population who did not have the intercurrent events

Estimand strategies

5. While-on-treatment strategy
    - Describe treatment effect before any intercurrent events occurred
    - Outcomes until the time of intercurrent events are analysed

Estimands in Diabetes Clinical Trials

- Attributes of Estimand in context with Diabetes trials
- Estimand strategies in context with Diabetes trials
- Example of Diabetes Clinical Trials using Estimand frame work


Change in HbA1c from baseline at 26 weeks
Variable of interest
Glucose lowering medicine under investigation
Treatment
ESTIMAND
Adult patients with type 2 diabetes
Population
Handling of intercurrent events
Rescue medication
Premature discontinuation
Loss to follow-up
Death
Mean difference between treatment groups
Summary measure

RCT (Drug A and Placebo) Diabetes Clinical Trial in Patients with T2DM controlled with diet and lifestyle

Population of interest	Adult patients with T2DM controlled with diet and lifestyle
Treatment description	New glucose lowering medication (Drug A) versus Placebo
Variable of interest	Primary Endpoint: Change in HbA1c from baseline at 26 weeks
Handling intercurrent events	1. Hypothetical Estimand → Measure effect if all patients had continued using trial product and did not use rescue medication. 2. Treatment Policy Estimand → Measure treatment effect regardless of trial product discontinuation or use of rescue medication. 3. Composite Estimand → Measure difference in proportion of patients who reached an absolute HbA1c value of ≤6.5 % at end-of-trial without rescue medication and who adhere to the trial product.

Why does it matter?

- Different results on the same endpoint may cause confusion

- Important to ask:

What scientific question and estimand do the results address?

PIONEER Programme

- Global Phase 3 trials for oral semaglutide involving >9000 patients with type 2 diabetes
- Included 10 trials
- Employed two estimands:
  - Treatment policy estimand
  - Trial product estimand

PIONEER 1: 26-week, randomized, double-blind, placebo-controlled, parallel-group trial conducted at 93 sites across 9 countries (identifier NCT02906930)

Trial Objective

To compare the efficacy and safety of oral semaglutide, as monotherapy with placebo in patients with type 2 diabetes

Estimand

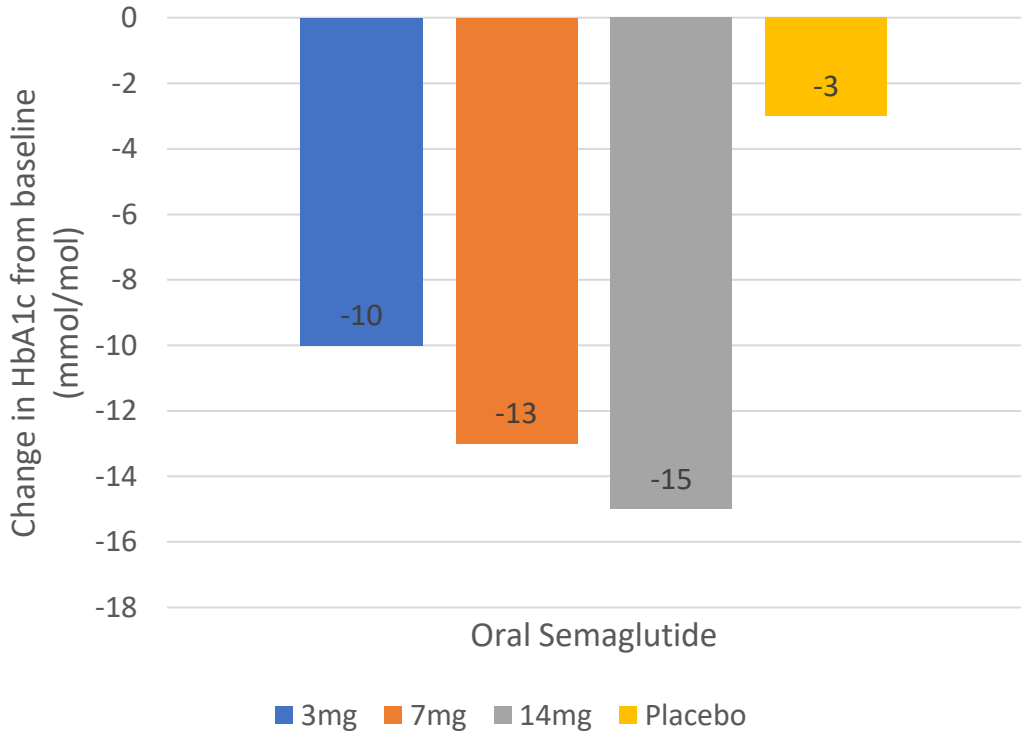
Two estimands addressed two efficacy-related questions

Treatment Policy Estimand (Regardless of trial product discontinuation or rescue medication use)

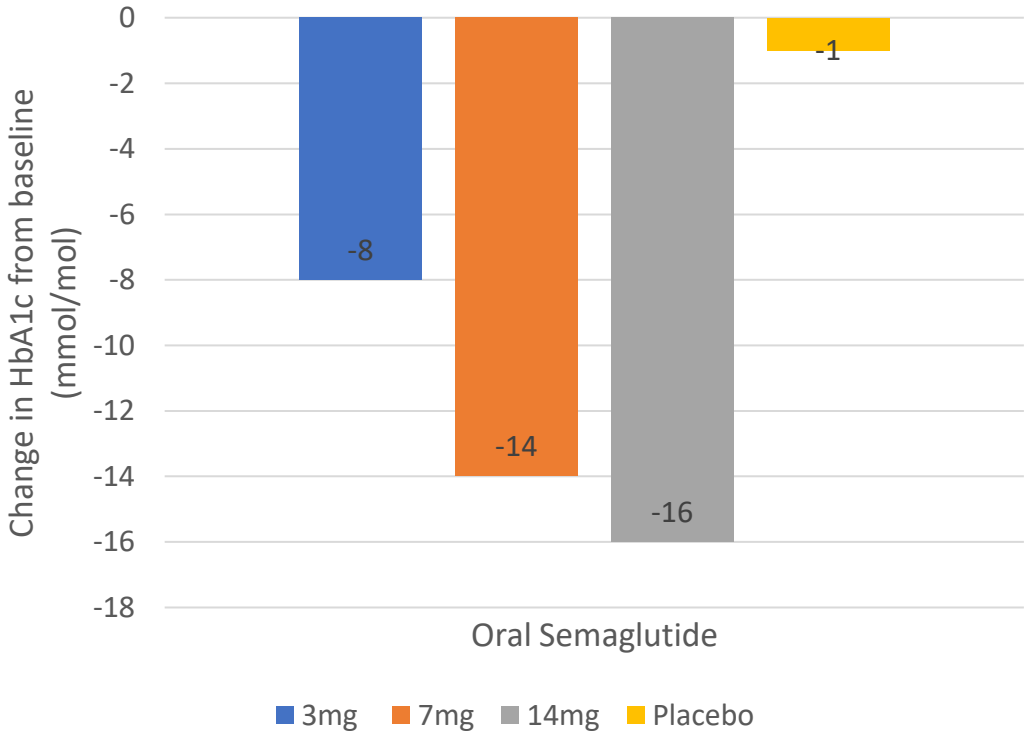
Trial Product Estimand (On trial product without rescue medication use)

PIONEER 1
Primary endpoint: Change in HbA1c from baseline to week 26

Treatment policy estimand



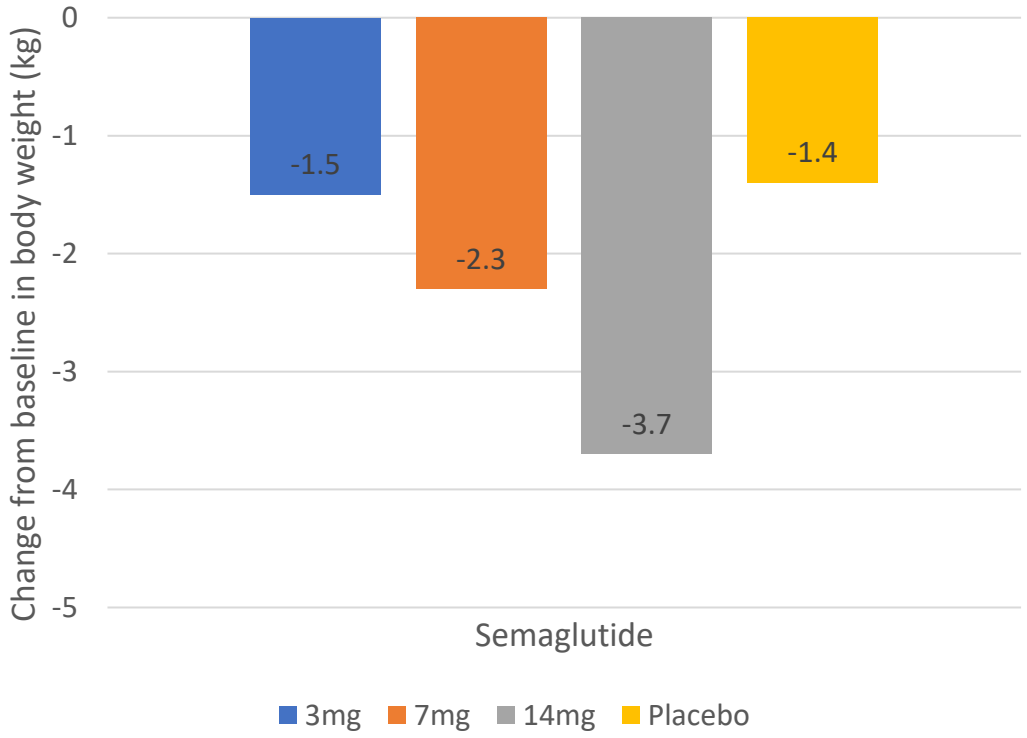
Trial product estimand



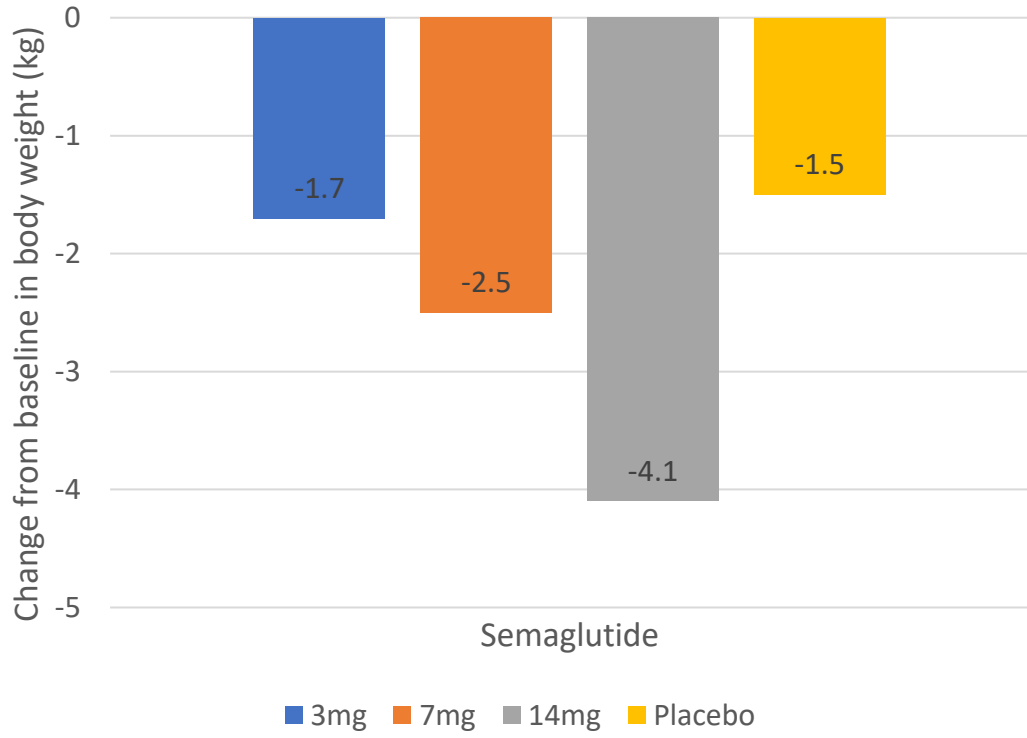
(Aroda et al. 2019)

PIONEER 1
Secondary endpoint: Change in body weight from baseline to week 26

Treatment policy estimand



Trial product estimand



Different estimands address different scientific questions.

- Hypothetical estimand (trial product estimand) will inform clinicians the glucose lowering effect of a new treatment if the patient is willing and able to take the new treatment as directed.

- Treatment policy estimand will describe how the treatment will work in a more real-life setting where treatment discontinuation and add-in therapies are common.

- Composite estimand might seek to combine these facets: proportion of patients reaching glycaemic targets while adhering to the trial product and not taking additional therapy.

Thank you!