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How the ICH E9 addendum around estimands may impact our clinical trials

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Introduction

- Draft E9 addendum has just been released
  - Significant impact on our work which requires a change of mindset
  - It proposes a framework for treatment effects to be more precisely specified, facilitating discussion between sponsor and regulator
- "Estimand" is not a statistical topic, rather a "drug development" topis
- Regulatory agencies are adopting the estimand framework
  - Increasing number of requests
  - Impact on design and conduct of new trials
  - Impact on answering regulatory questions for ongoing programs
- Failure to adequately address estimand questions can have severe consequences in our trials

Treatment effect

[Section A.3.1]

How does the outcome of treatment compares to what would have happened to the same patients under different treatment conditions (e.g. had they not received the treatment or had they received a different treatment).

Treatment effect

Suppose there are two treatments, A (active) and B (placebo).

Hypothetical scenario: We know the outcome for each patient under both treatment conditions, A or B

- Patient 1 is perfectly adherent to whichever treatment s/he is assigned. The outcome is 9 on treatment A or 8 on treatment B.

  What is the treatment effect?

- Patient 2 adheres to treatment B with an outcome of 7, but discontinues if assigned to A (e.g. due to adverse events).

  What is the treatment effect?

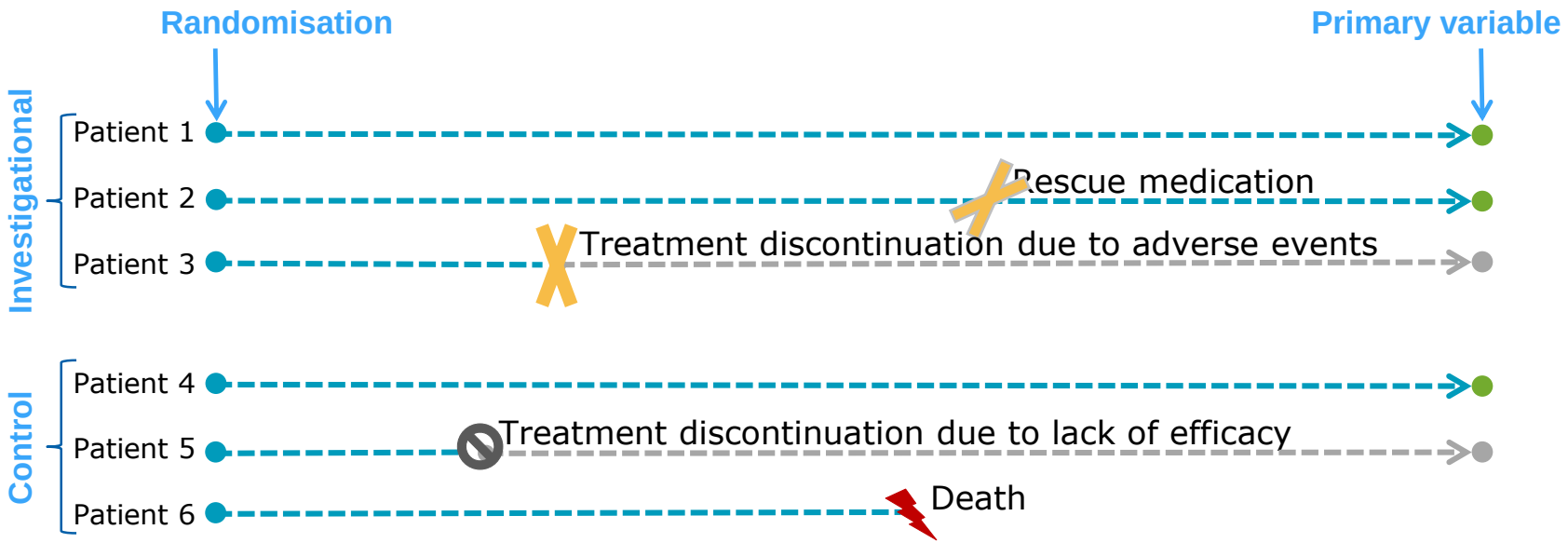
- Patient 3 adheres to treatment A with an outcome of 7, but discontinues if assigned to B (e.g. due to lack of efficacy) and takes rescue medication, with an outcome of 6 in the end.

  What is the treatment effect?

Treatment effect

Patients differ in response to treatment due to the occurrence of events after randomization ("intercurrent events")

- Some patients will tolerate a medicine and adhere to its administration schedule, others will not
- Some patients will require additional medication, others will not
- …



How to define the treatment effect in the population of interest for the primary variable in the presence of intercurrent events?

Intercurrent events

[Section A.3.1]

- Intercurrent events can present in multiple forms and can affect the interpretation of the outcome. For example,
  - if a patient dies before a planned measurement of blood pressure, the blood pressure will not be observed
  - if a patient takes rescue medication in addition to treatment, the blood pressure may be observed, but will reflect the combined effect of the treatment and the rescue medication
  - if a patient discontinues treatment because of adverse events, the blood pressure may be observed but will reflect the lack of effect of the treatment when it is not taken

Intercurrent events

- Intercurrent events need to be considered in the description of a treatment effect on a variable of interest because both the value of the variable and the occurrence of the event may depend on treatment.
- The definition of a treatment effect should consider whether values of the variable after an intercurrent event are relevant, as well as how to account for the (possibly treatment-related) occurrence or non-occurrence of the event itself.

Dapagliflozin – for illustration

- Primary variable: Change in HbA1c from baseline to 24 weeks.
- Sponsor proposal: Data after initiation of rescue medication was excluded from the analysis.
- *"While FDA has implicitly endorsed LOCF imputation for diabetes trials in the past, there is now more awareness in the statistical community of the limitations of this approach.* Instead I have included a sensitivity analysis in which the primary HbA1c outcomes are used regardless of rescue treatment, and no statistical adjustment is made for rescue. *This approach is also imperfect, but it comes closer to being a true intent-to-treat (ITT) analysis ..."*

Dapagliflozin – for illustration

Different perspectives on the inclusion of data

- Sponsor: Remove data after initiation of rescue medication

- FDA: Include all data regardless of initiation of rescue medication

Dapagliflozin – for illustration

Implied 'scientific questions [illegible]':

- Sponsor: Attempt to estab[illegible] effect of the initially randomized treatments[illegible] rescue medication;
- FDA: Compare treatment[illegible]in plus rescue' versus 'control plus rescue'.

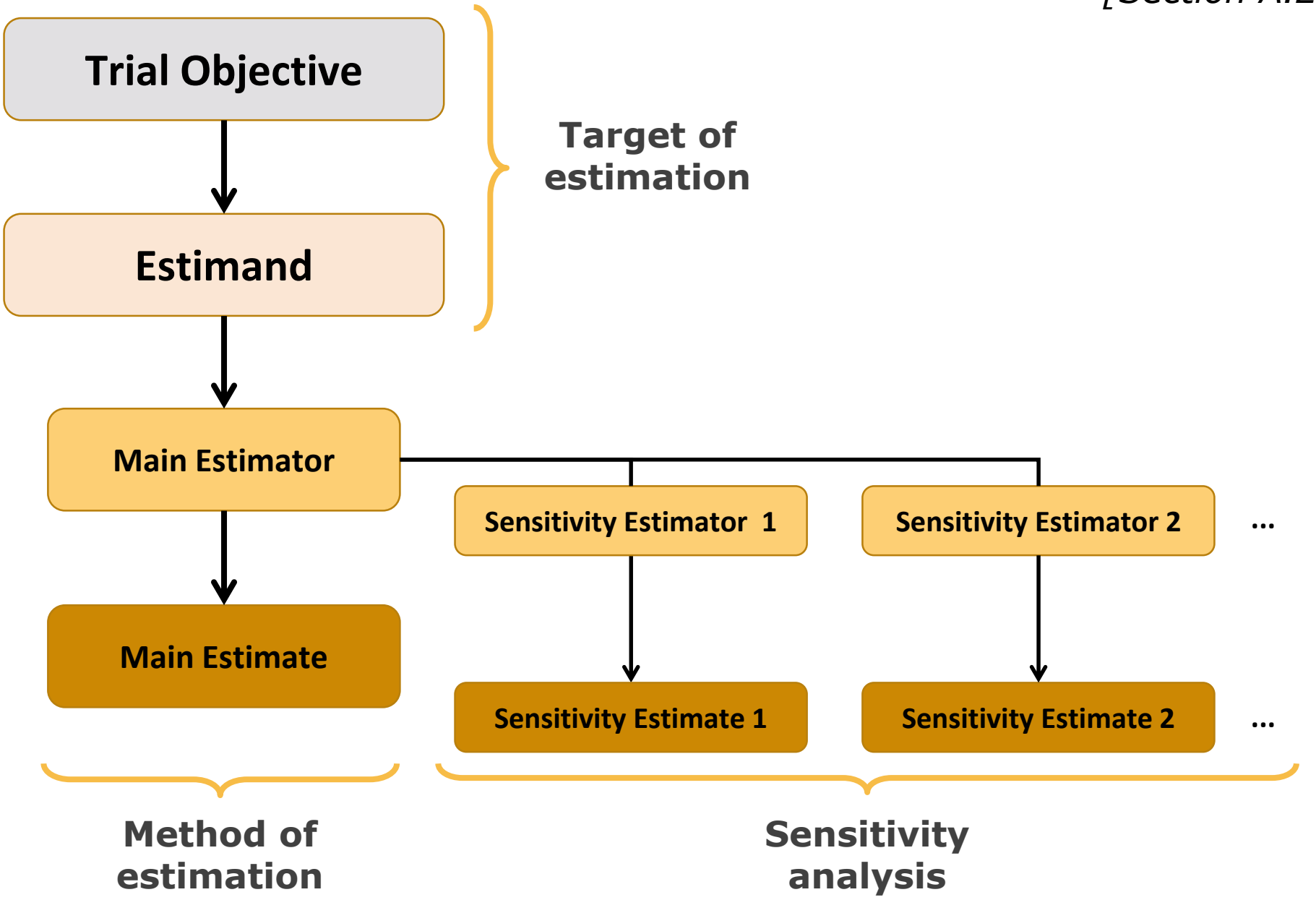
Disagreement over what to estimate; <u>the estimand</u>.

ICH E9(R1)

- More than one 'treatment effect' can be described and estimated, raising questions like:
  - What is of interest for regulatory decision making?
  - What do we need to communicate to prescribers?
  - Can we estimate those?
- These types of problems became so prevalent that it was suggested as a topic for an ICH guideline
  - An ICH E9 addendum on "Estimands and Sensitivity Analysis in Clinical Trials" was endorsed in 2014 and just released as E9(R1) for publication consultation
- This addendum helps aligning trial objectives with analysis methods in a coherent way, allowing for more informed discussions with regulatory agencies

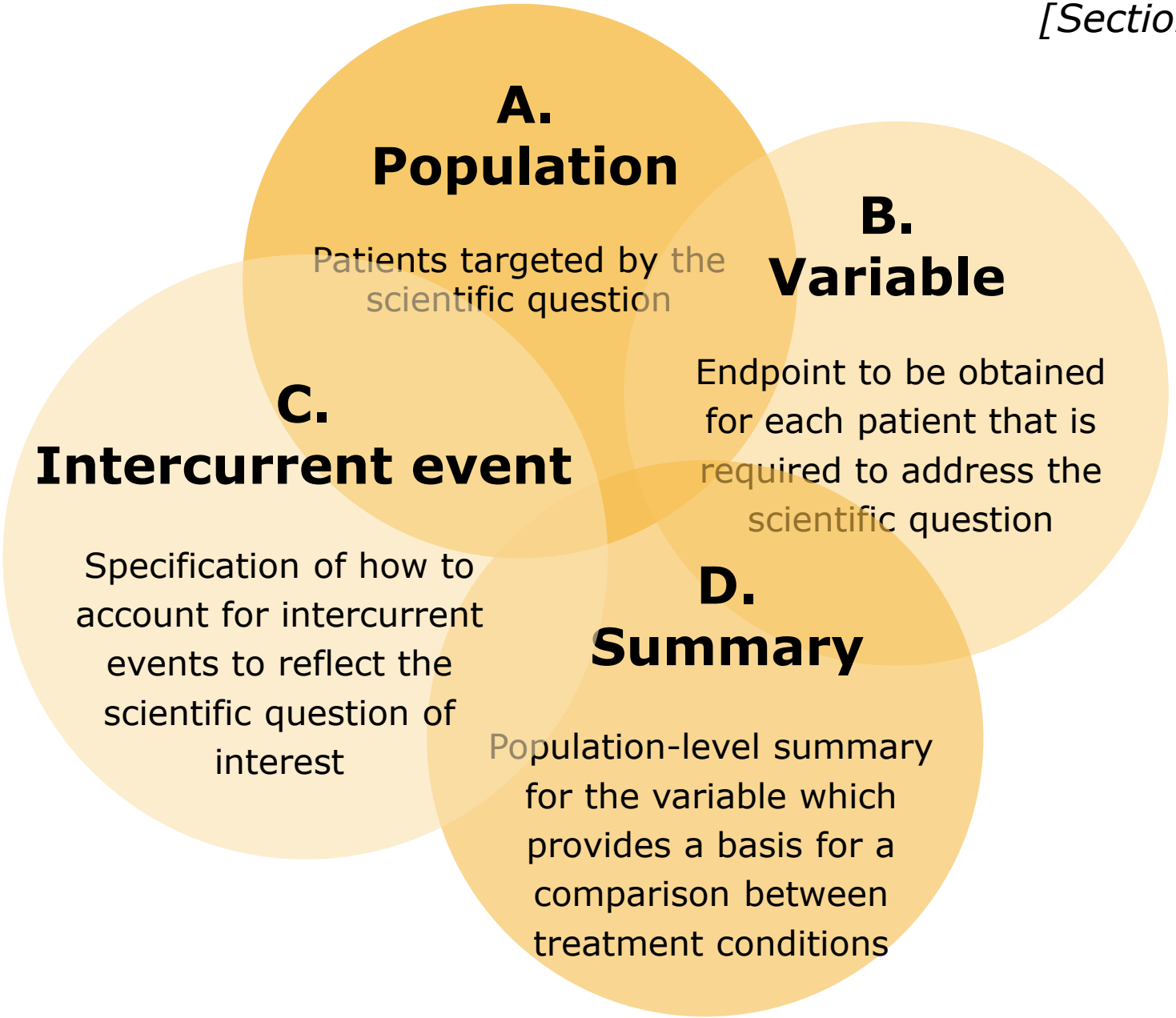
A new framework

[Section A.2]



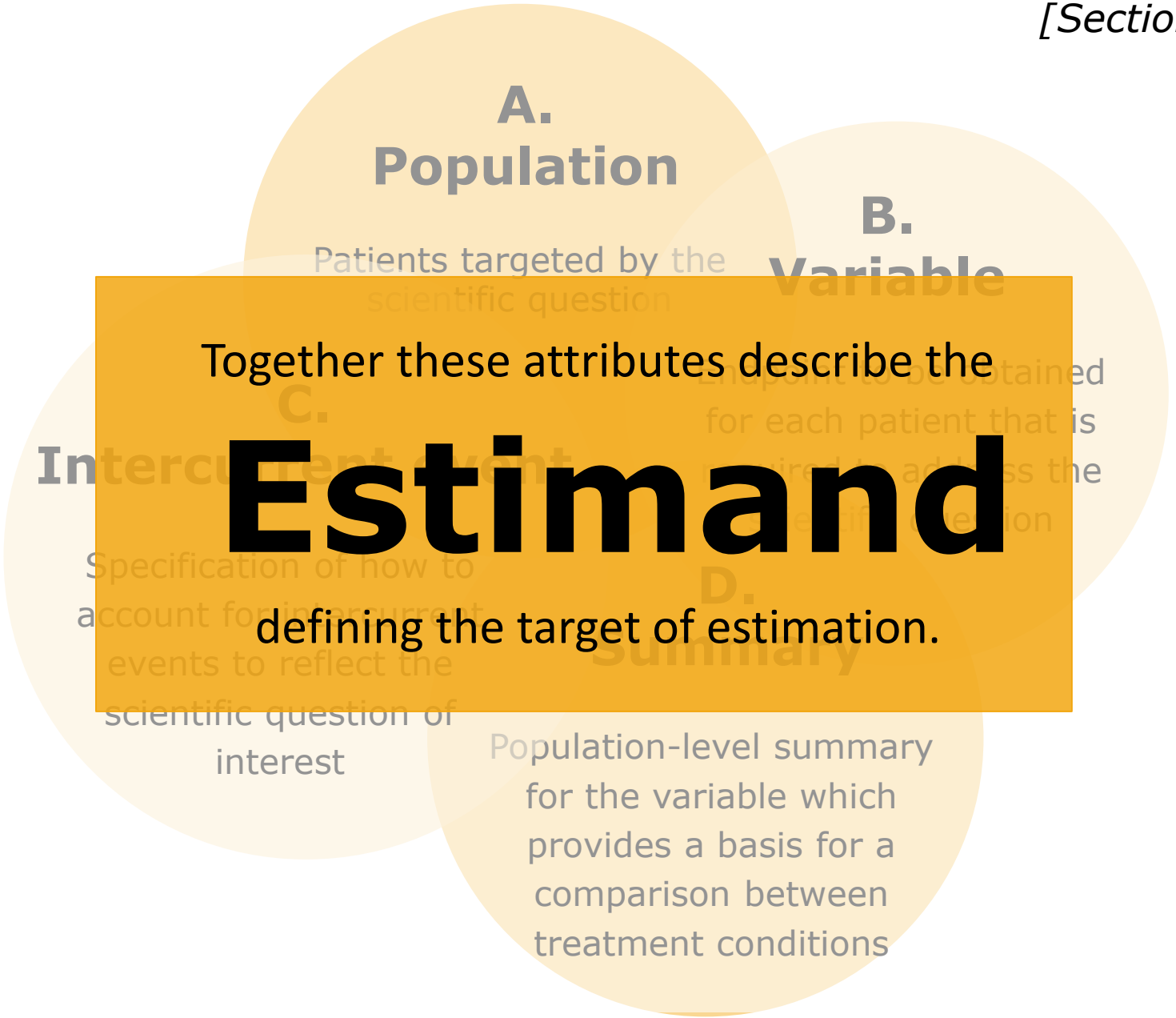
Estimand description

[Section A.3.1]



Estimand description

[Section A.3.1]



Estimand strategies

[Section A.3.2]

Altogether, five different strategies are considered. It is important to be precise when describing the preferred strategy for handling each intercurrent event.

1. **Treatment policy strategy:** The occurrence of the intercurrent event is irrelevant: the value for the variable of interest is used regardless of whether or not the intercurrent event occurs.
2. **Composite strategy:** The occurrence of the intercurrent event is taken to be a component of the variable, i.e. the intercurrent event is integrated with one or more other measures of clinical outcome as the variable of interest.
3. **Hypothetical strategy:** A scenario is envisaged in which the intercurrent event would not occur: the value to reflect that scientific question of interest is that which the variable would have taken in the hypothetical scenario defined.
4. **Principal stratum strategy:** The target population might be taken to be the principal stratum in which an intercurrent event would not occur. For example, the target population of interest might be taken to be the stratum of patients in which failure to adhere to treatment would not occur. In other words, a principal stratum is a subset of the broader population who would not experience the intercurrent event. The scientific question of interest relates to the treatment effect only within that stratum.
5. **While on treatment strategy:** Response to treatment prior to the occurrence of the intercurrent event is of interest. If a variable is measured repeatedly, its values up to the time of the intercurrent event may be considered to account for the intercurrent event, rather than the value at the same fixed timepoint for all subjects.

Real examples

- Example 1: Palliation in terminally ill cancer patients

  (based on work/slides by Rob Hemmings, MHRA)
- Example 2: Treatment of chronic pain

  (based on work/slides by Francesca Callegari, Novartis)

Example 1 – Background (simplified)

- Consider a new Drug X for palliation in terminally ill cancer patients. Symptomatic treatment a priori not expected to beneficially or detrimentally effect mortality.
- Response on body weight and functioning are assessed after 12 weeks
- Scientific question of interest concerns the comparison in a randomized trial of Drug X to placebo.
- Some patients will die during the 12-week follow-up. This is the intercurrent event.
- Anti-cancer therapy used as background therapy in both treatment groups.

Example 1 – No intercurrent events

A. **Population**: defined through appropriate inclusion/exclusion criteria to reflect the targeted patient population for approval

B. **Variable**: change from baseline after 12 weeks

C. **Intercurrent events**: not expected to occur

D. **Summary measure**: difference in variable means

Unrealistic not to expect any deaths

Example 1 – Treatment policy

A. **Population**: defined through appropriate inclusion/exclusion criteria to reflect the targeted patient population for approval
B. **Variable**: change from baseline after 12 weeks
C. **Intercurrent events**: Regardless of death
D. **Summary measure**: difference in variable means

How to measure response on body weight and functioning after death?

Example 1 – Composite

A. **Population**: defined through appropriate inclusion/exclusion criteria to reflect the targeted patient population for approval

B. **Variable**: binary; alive and with maintenance of weight/functioning after 12 weeks

C. **Intercurrent events**: captured through the variable definition

D. **Summary measure**: difference in response proportions

Viable, but is it really a treatment failure if a patient lived reasonably well throughout 11 weeks and then dies?

Example 1 – Hypothetical

A. **Population**: defined through appropriate inclusion/exclusion criteria to reflect the targeted patient population for approval
B. **Variable**: change from baseline after 12 weeks
C. **Intercurrent events**: had the patient not died
D. **Summary measure**: difference in variable means

How would a hypothetical scenario look like: Would the patient have continued treatment? Or discontinued treatment?

Example 1 – Principal stratum

A. **Population**: defined through subjects alive after 12 weeks, within the targeted population defined by inclusion/exclusion criteria
B. **Variable**: change from baseline after 12 weeks
C. **Intercurrent events**: captured through the population definition
D. **Summary measure**: difference in variable means

Viable, but aren't we intrested in assessing the treatment effect even in those patients who died prior to week 12?

Example 1 – While on treatment

A. **Population**: defined through appropriate inclusion/exclusion criteria to reflect the targeted patient population for approval
B. **Variable**: area under the curve for weight/functioning while being on randomised treatment
C. **Intercurrent events**: captured through the variable definition
D. **Summary measure**: difference in variable means

Reasonable estimand?

Example 1 – Background (extended)

In reality, three relevant types of intercurrent events may occur:

- death
- change in background anti-cancer medicine;
- use of additional symptomatic medication.

The construction of an estimand should address each intercurrent event that may occur in the clinical trial and that will affect the interpretation of the results of the trial.

Example 2 – Background

- Consider a new Drug X for patients suffering from chronic pain.
  - Includes chronic pain from different etiologies, such as cancer pain, postsurgical or posttraumatic pain, neuropathic pain etc.
- Measured on an 11–point Numerical Rating Scale (NRS) for patient self-reporting of pain
- Scientific question of interest concerns the comparison in a randomized trial of Drug X to placebo
- Some patients will face intercurrent events not leading to study treatment discontinuation, but with potential confounding effects
  - E.g. changes in doses of allowed concomitant medications for pain
- Other patients will face intercurrent events leading to study treatment discontinuation
  - E.g. adverse events, lack of efficacy, use of other concomitant medications or due to other reasons

Example 2 – Scientific question of interest

- Scientific question of interest guiding the primary estimand:

  Estimate the treatment effect of Drug X against placebo for the target population on the primary variable. The treatment effect of interest shall

  - be unconfounded by events which are deemed non-informative, e.g. changes in doses of allowed concomitant medications for pain
  - account for the unfavorable outcome when patients are unable to continue taking the study drug due to an adverse event, lack of efficacy or use of other concomitant medications leading to study treatment discontinuation.

Example 2 – Primary estimand

Key attributes

A. **Population**: Patients suffering from the chronic pain condition at a moderate to severe disease stage. Patients may or may not be already on a concomitant medication for pain.

B. **Variable**: Change from baseline to last week of the study in weekly mean of the 24h average pain score measured by NRS

C. **Intercurrent events**: Events happening post-randomization, which can be an expression of how well the treatment works, but also of its safety and tolerability

D. **Summary measure**: Difference of variable means between Drug X and placebo

Example 2 – Primary estimand

Details on attribute C

We are interested in the treatment effect if patients:

- would not change dose of allowed concomitant medications for pain
- are allowed to take short-acting pain relief medication
- would continue to be treated for the entire study duration unless forced to discontinue treatment due to
  - adverse events (AEs)
  - lack of efficacy (LoE)
  - use of other concomitant medications leading to treatment discontinuation

Example 2 – Primary estimand

Justification

Desire to quantify the treatment effect of the study drug under the situation where:

- any potential confounders are removed, since these could lead to an attenuation or a dilution of the treatment effect of interest
- the drug is taken for the stipulated duration, however
- we cannot ignore the situations when a patient can no longer tolerate or benefit from the treatment (e.g. occurrence of AE, LoE etc), from whom a continuation of treatment would not be conceivable
- other patients who discontinued the drug due to other reasons could have theoretically continued to be treated without being put at undue risk

Example 2 – Further considerations

Statistical analysis

- Primary analysis approach is in line with the primary estimand, including handling of changes in doses of allowed concomitant medication for pain and handling of missing data due to study treatment discontinuation
- Sensitivity analysis targets the same estimand and is specified to assess the robustness of conclusions from the primary analysis
- Supplementary analysis for a broader understanding of the treatment effect

Necessary design features

- Information on changes in dose of allowed concomitant medications for pain
- Retrieved dropouts: data collected after study treatment discontinuation, if available

A new framework

Streamlined thinking for enhanced interaction, a common language.

- Interaction between statisticians and clinicians.
  - Some decisions should not be taken at the level of the statistical analysis, but before ➔ estimand;
  - Description of estimand and choice of strategy are based on the clinical setting, mainly a clinician's decision;
  - The statistician should highlight when an estimand is difficult or impossible to estimate.

A new framework

Streamlined thinking for enhanced interaction, a common language.

- Interaction between sponsor and regulators.
  - Framework will assist sponsor to design clinical trials;
  - And regulators for assessment.

Questions…