



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

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
- 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 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?

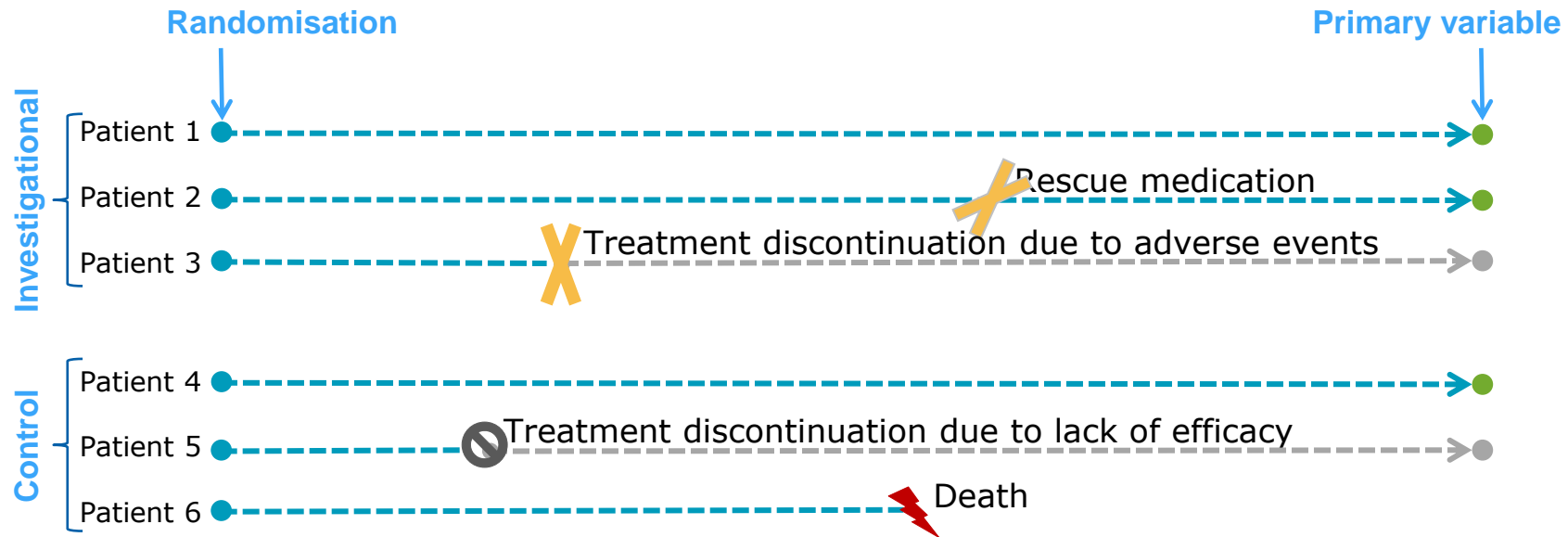
- **Patient 3** adheres to treatment A with an outcome of 7, but discontinues if assigned to B (e.g. due to lack of efficacy) and takes rescue medication, with an outcome of 6 in the end.

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':

- **Sponsor:** Attempt to estimate treatment effect of the initially randomized treatments and rescue medication;
- **FDA:** Compare treatment 'dapagliflozin plus rescue' versus 'control plus rescue'.



Disagreement over what to estimate; the estimand.

Dapagliflozin – for illustration

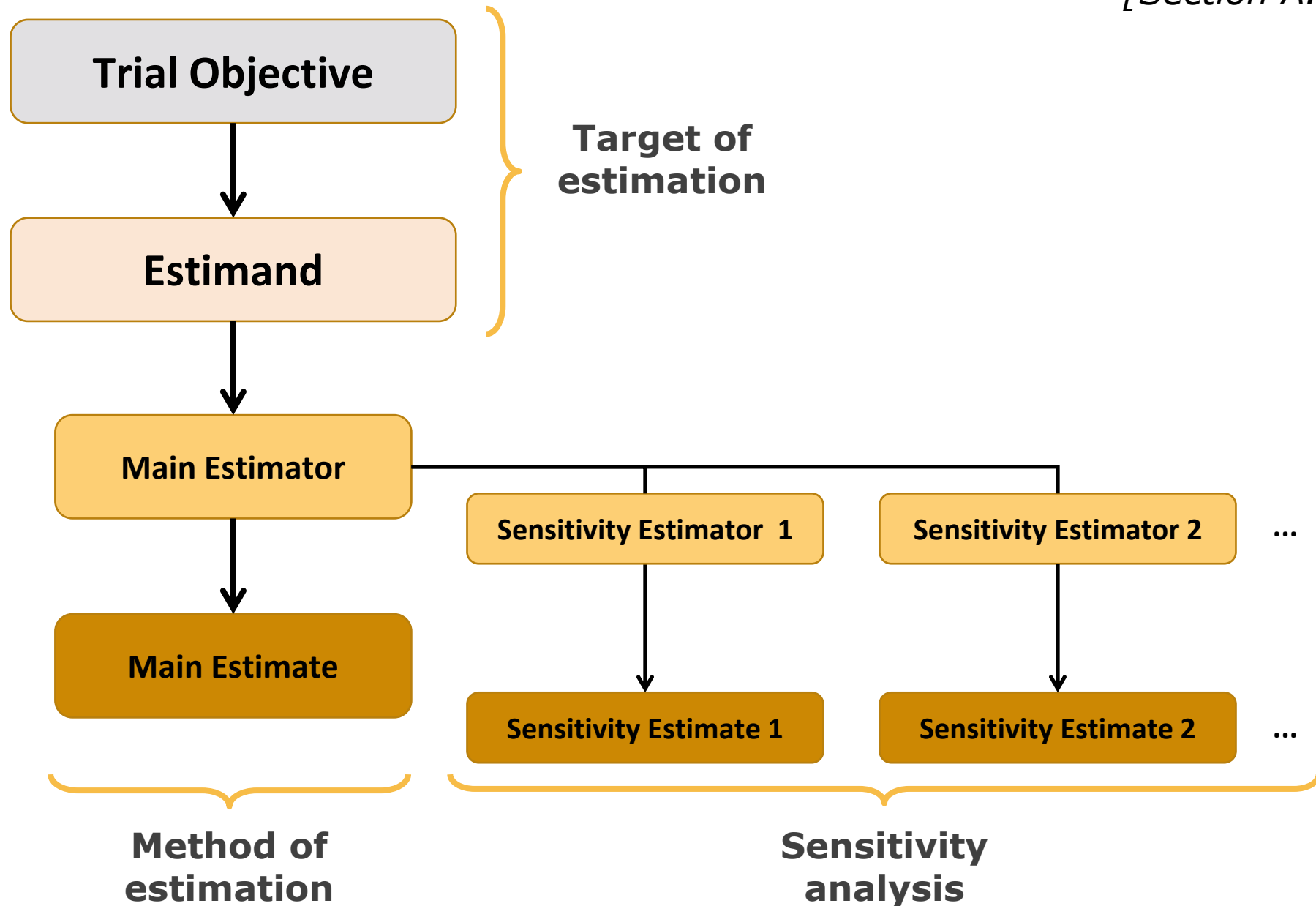
- In this case the description of the treatment effect needs to account for the **use of rescue medication** as an intercurrent event.
- **Two strategies** are described that implicitly define different treatment effects:
 - “effect **if no rescue medication had been used**” (sponsor)
 - “effect **regardless of whether rescue medication is used**” (FDA)
- More generally,
 - ... the sole focus is on particular techniques and the assumptions required in order that they give reliable estimates.
 - Statisticians have long discussed ‘missing data’. Old methods were criticised; new methods introduced ... then criticised.
 - ... the conversation between sponsor and FDA was **imprecise**, but ultimately necessary.
 - Didn’t recognize that some of the ‘missing data’ were not in fact missing.
 - The meaning of ‘intention to treat’ had become obscured.

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

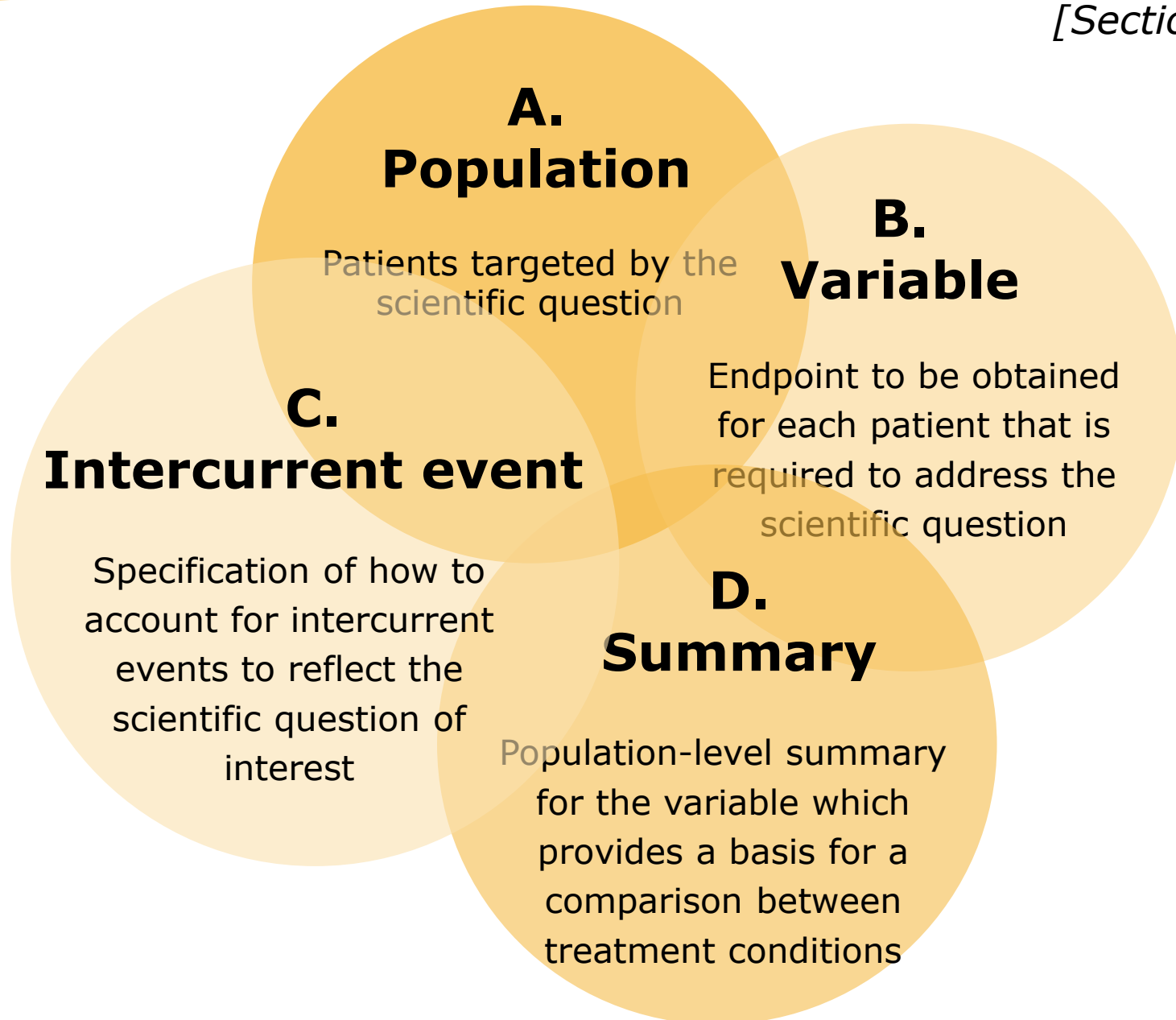
A new framework

[Section A.2]



Estimand description

[Section A.3.1]



Estimand description

[Section A.3.1]

A. Population

Patients targeted by the scientific question

B. Variable

Supportable data obtained for each patient that is required to address the scientific question

C. Intercurrent events

Specification of how to account for intercurrent events to reflect the scientific question of interest

D. Summary

Population-level summary for the variable which provides a basis for a comparison between treatment conditions

Together these attributes describe the

Estimand

defining the target of estimation.

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.

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...

