ASA CT chapter - Academic Webinar Series
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How the ICH E9 addendum around estimands may impact our clinical trials

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Disclaimer

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Problem statement

- Can you (Do you) define precisely the treatment effect that your clinical trial will estimate?
- Our tenet and motivation is that this is not done, or is done inadequately, and that this lack of clarity causes difficulties.
- Current practice is for the data collection and the analytical approach to define which 'treatment effect' is being estimated. This order needs to be reversed.

Problem statement

- We propose a framework for treatment effects to be more precisely specified, facilitating discussion between sponsor and regulator.
- Today we will seek to:
  - convince you that the problem exists and is important;
  - describe the direction of travel of the ICH group charged with proposing a solution.

Treatment effect

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).

- 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.
  - Some patients will tolerate a medicine and adhere to its administration schedule, others will not;
  - Some patients will require additional medication, others will not.
- This introduces heterogeneity as to how patients respond to treatment and indicates that more than one 'treatment effect' can be described and estimated.
  - What is of interest for regulatory decision making?
  - What do we need to communicate to prescribers?
  - Can we estimate those?

Treatment effect

- Patients differ in response to treatment, also in clinical trials.
- Randomised trials are expected to be free from baseline confounding but, in trials as in clinical practice, certain events will occur that complicate the description and interpretation of treatment effects
- For today, these events are denoted as intercurrent events and include, among others
  - use of an alternative treatment (e.g. a rescue medication, a medication prohibited by the protocol or a subsequent line of therapy)
  - discontinuation of treatment
  - treatment switching
  - terminal events such as death

Intercurrent events

- 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

Treatment effect

- 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 est[illegible]ment effect of the initially randomized treatments[illegible] rescue medication;
- FDA: Compare treatme[illegible]lozin plus rescue' versus 'control plus rescue'.

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

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 recognise that some of the 'missing data' were not in fact missing.
    - The meaning of 'intention to treat' had become obscured.

ICH E9(R1)

- Need to link trial objectives and analysis methods in a coherent way
  - First, the relevant treatment effect to be estimated, i.e. the estimand, should be defined.
  - Subsequently, trial design, data collection and statistical analysis approaches have to be aligned with the estimand.
- 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.
  - Draft ICH E9(R1) guidance (to be) released in 2017 for publication consultation.

A new framework

Trial Objective

Estimand

Target of estimation

Current practice often not aligned with proposed framework

Main Estimator

Main Estimate

Sensitivity Estimator 1

Sensitivity Estimator 2

...

Sensitivity Estimate 1

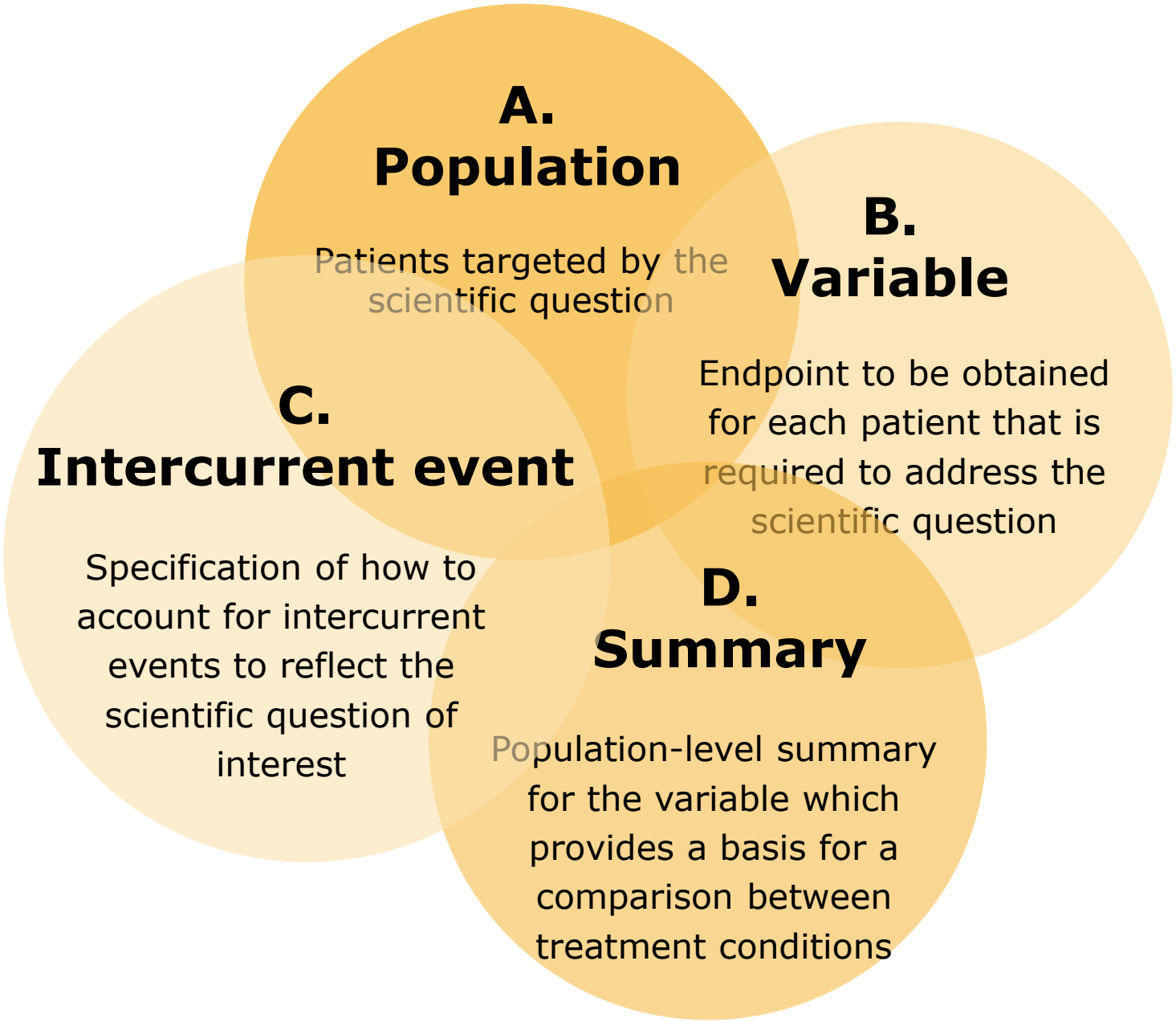
Sensitivity Estimate 2

...

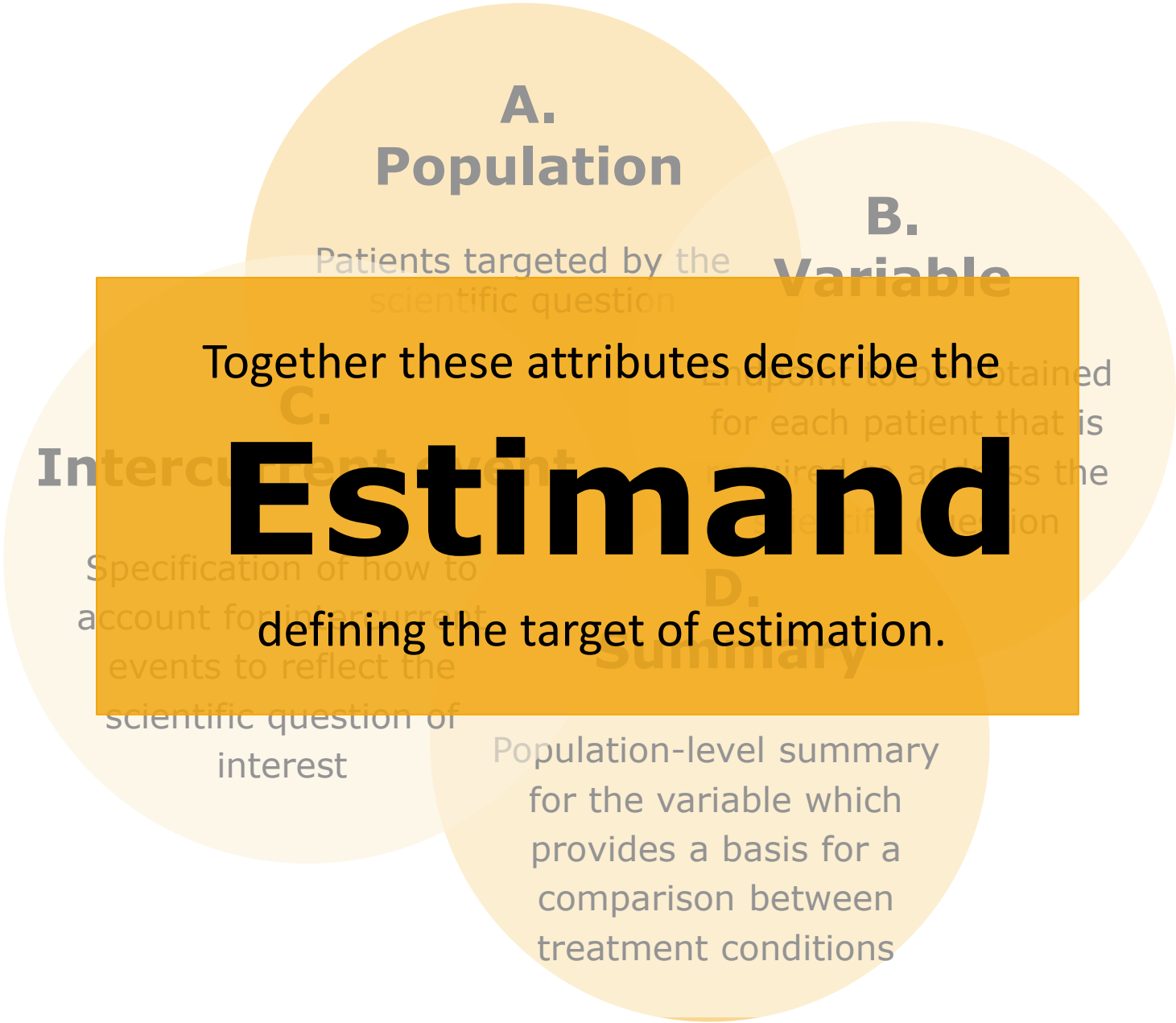
Method of estimation

Sensitivity analysis

Estimand description



Estimand description



Together these attributes describe the

Estimand

defining the target of estimation.

Estimand strategies

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…