Estimands and Sensitivity Analyses: What's in the new ICH E9 Addendum?

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Disclaimer

The views expressed are those of the presenters and should not be understood or quoted as being made on behalf of the International Conference on Harmonisation (ICH) or reflecting the position of the ICH or Amgen.

The E9 addendum [E9(R1)] is out for public consultation

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

30 August 2017
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Committee for Human Medicinal Products

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

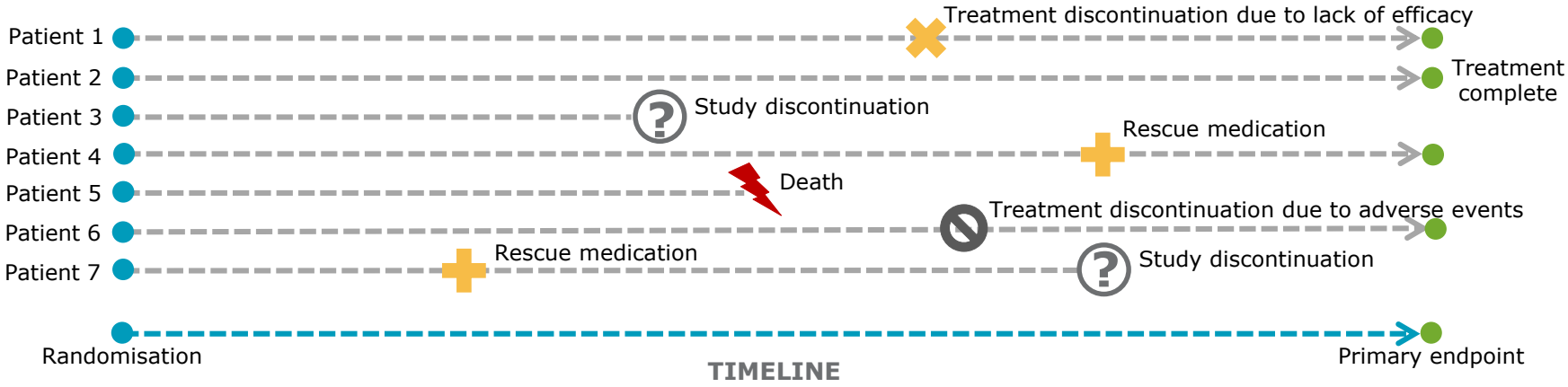
Step 2b

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

Agenda

- Motivation for ICH E9(R1)
- New framework
- Description of an estimand
- Strategies for handling intercurrent events
- Examples
- ICH E9(R1) table of contents
- Summary
- References

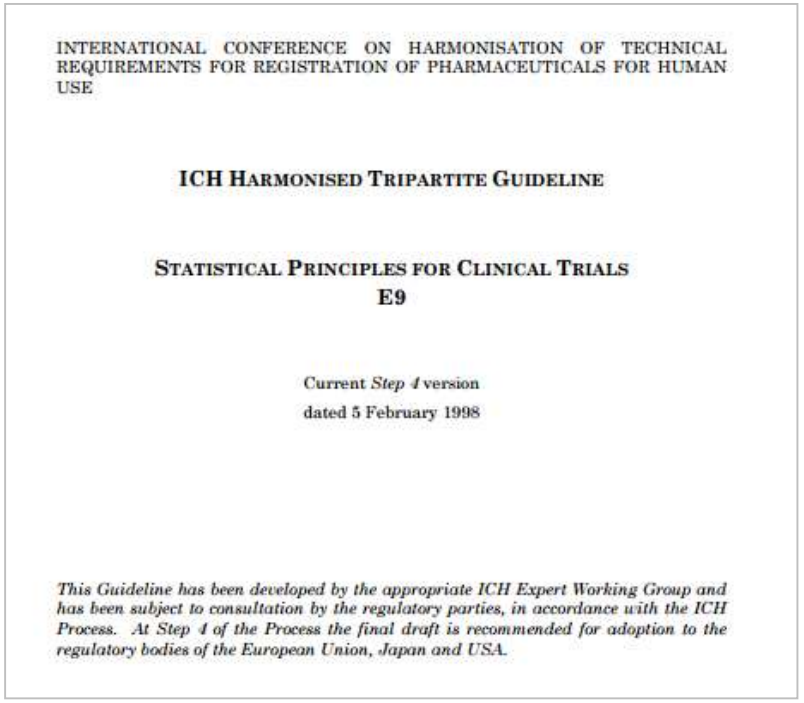
Intercurrent events



- Events may occur that make the relevance, the definition, or even the existence of the primary variable questionable.
- Such events may include: death, treatment discontinuation due to adverse events or lack of efficacy, use of other medicines affecting the outcome, whether specified or prohibited by the protocol.

What does ICH E9 say?

- "The principle that asserts that the effect of a **treatment policy** can be best assessed by evaluating on the basis of the **intention to treat** a subject (i.e. the planned treatment regimen) rather than the actual treatment given. It has the consequence that subjects allocated to a treatment group should be followed up, assessed and analysed as members of that group irrespective of their compliance to the planned course of treatment."



INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

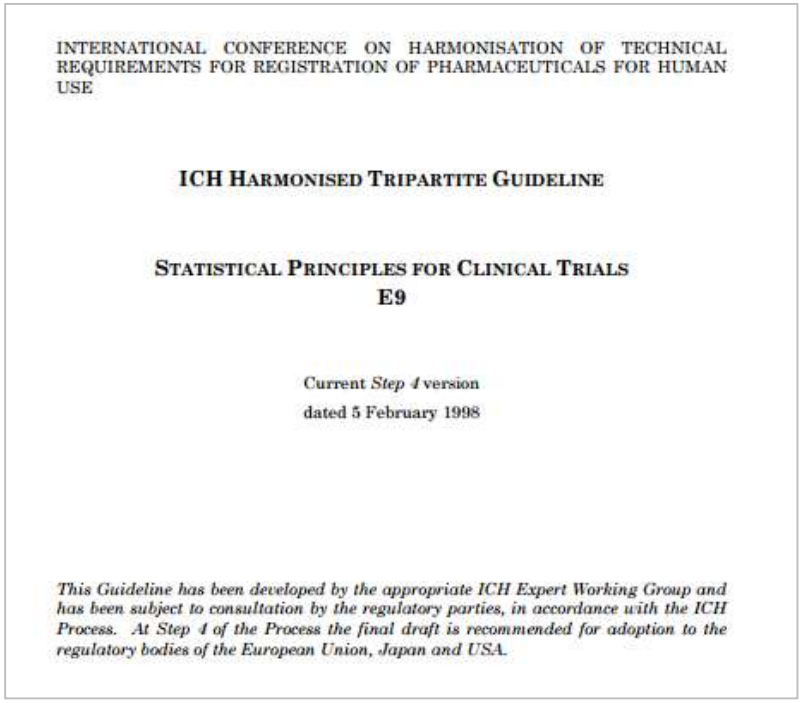
STATISTICAL PRINCIPLES FOR CLINICAL TRIALS
E9

Current *Step 4* version
dated 5 February 1998

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

What does ICH E9 say?

- "The ITT principle implies that the primary analysis should include all randomised subjects. (…) Preservation of the initial randomisation in analysis is important in preventing bias and in providing a secure foundation for statistical tests. (…) Under many circumstances the full analysis set may also provide estimates of treatment effects likely to mirror those in practice."



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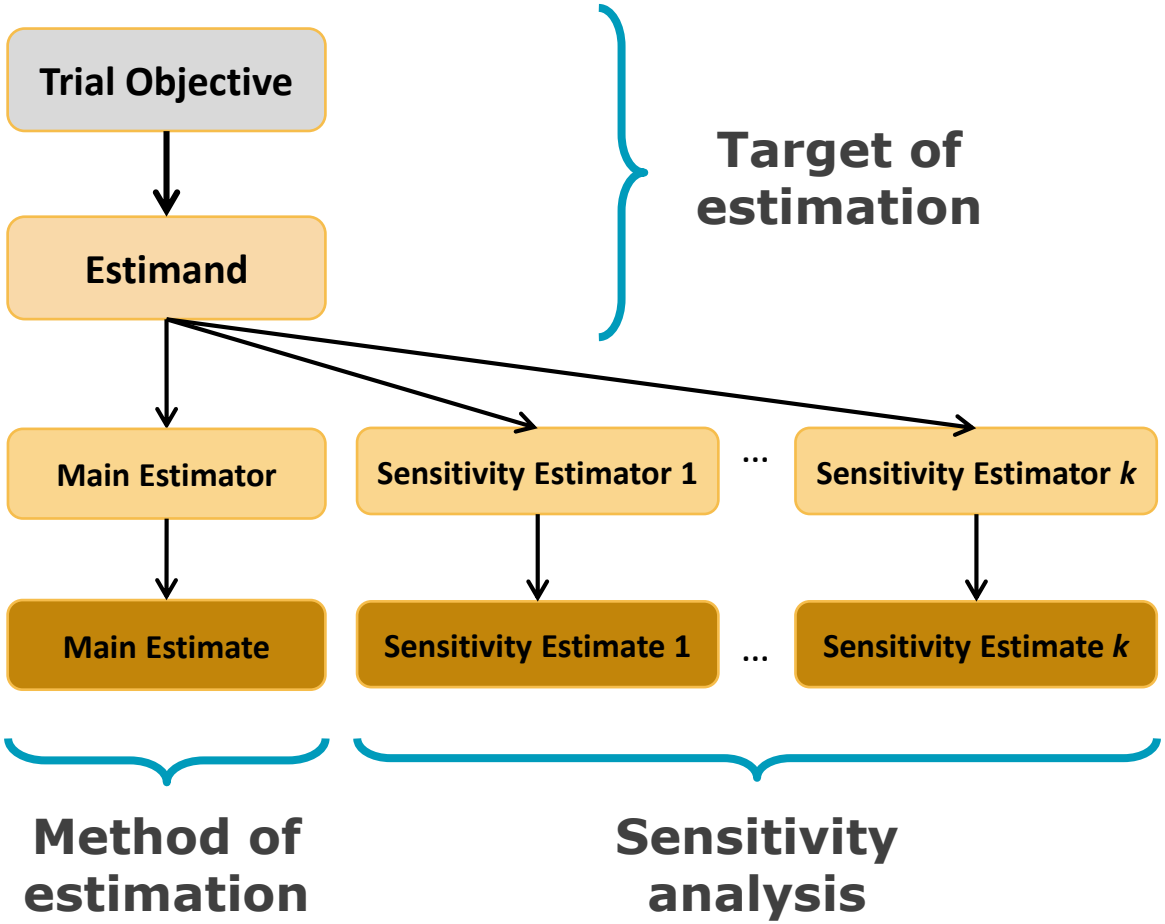
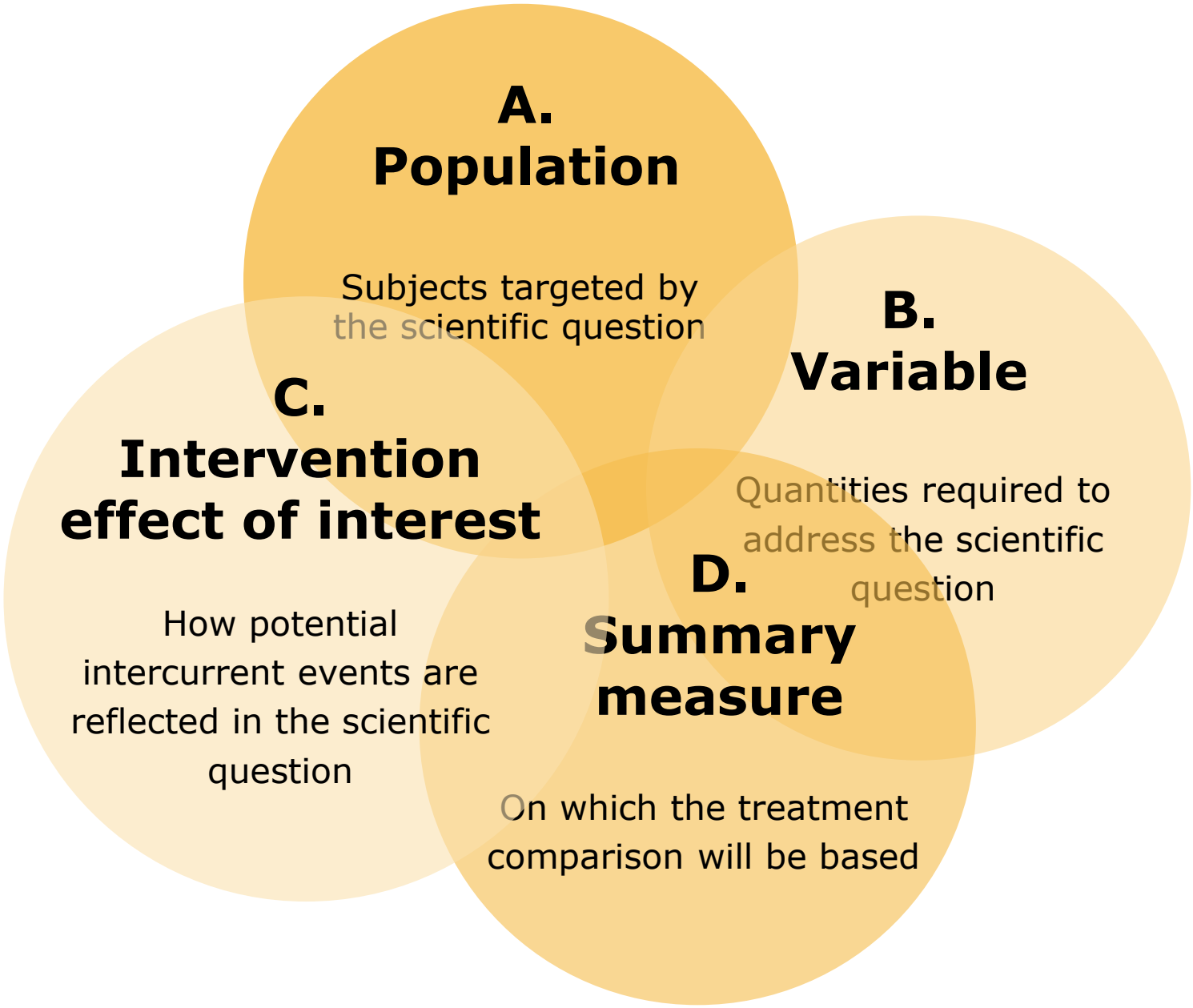
A new framework



Description of an estimand



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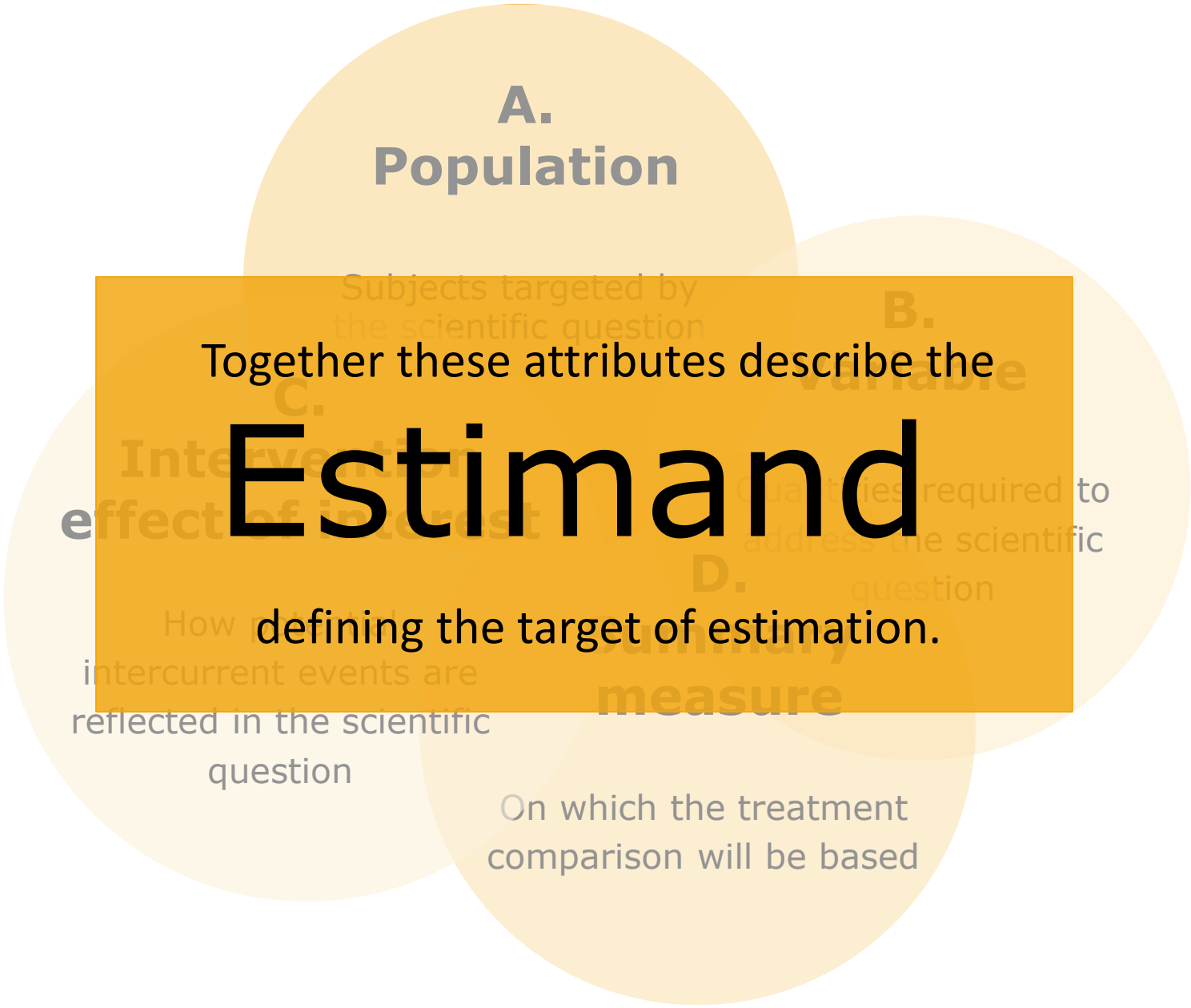

Together these attributes describe the

Estimand

defining the target of estimation.

Strategies for addressing intercurrent events

- Any estimand description will not be complete without attention to the handling of intercurrent events;
  - Such events may make the variable nonexistent, unobservable, or possibly irrelevant.
- At least **five strategies** may be considered to account for intercurrent events, to be used alone or in combination;
  - These strategies address the estimands attributes A – D, possibly in a complex way.

1. 'Treatment-policy'

- Actual values of the variable regardless of whether the intercurrent event has occurred.
  - May be relevant if a value for the variable is meaningful notwithstanding an intercurrent event.
  - Inference can be complemented by defining an additional estimand and analysis pertaining to the intercurrent event itself.
  - No estimand based on actual values can be properly defined when the actual values do not all exist;
    - In particular, a treatment-policy strategy is meaningless with respect to values of a variable not obtained due to death.

2. 'Composite' or 'transformed'

- Modified definition of the variable or the summary measure such that an intercurrent event becomes a component of the outcome.
- Particularly relevant if the intercurrent event is itself the most meaningful outcome that can be observed, e.g.
  - The fact that a patient has died may be much more meaningful than observations before death, and observations after death will not exist;
  - Discontinuations of treatment for lack of efficacy or for AEs may provide meaningful information on the drug effect, even though they do not yield a numerical value for the intended variable.

3. 'Hypothetical'

- Values of the variable under some hypothetical conditions where an intercurrent event would not happen.
- Care is required to clearly describe the hypothetical conditions defining the estimand.
- Some hypothetical conditions are likely to be more acceptable than others, e.g.
  - When rescue medicine must be given for ethical reasons, the scientific question concerning the outcome if rescue had not been given may be an important one;
  - The question of what would have happened if patients, who discontinued treatment because of AEs, had not had those AEs may not be of scientific or regulatory interest.

4. 'Principal strata'

- Restrict population of interest to the stratum of patients in which an intercurrent event would not have happened.
- Such strategy is not to be confused with a 'complete case' analysis;
  - For example, it might of interest to demonstrate a benefit among those patients who would not experience AEs leading to treatment discontinuation;
  - This is one interpretation of a per-protocol analysis but such an estimand cannot in general be estimated without severe bias merely by analysing a per-protocol data set.

5. 'While on treatment'

- Values of the variable up to the time of the intercurrent event, rather than at the planned assessment point.
- May be of relevance in longitudinal studies if the same variable is measured repeatedly.

The construction of an estimand should be…

- **consequent to the trial objectives** and should precede choices relating to data collection and analytic approaches.
- **clinically interpretable**, in terms of the population and endpoint, but also in terms of the intervention effect of interest and, finally, the summary measure.
- duly justified **considering the therapeutic setting** and the treatment goals of the intervention, from which the key scientific questions of interest can be derived.
- a **multi-disciplinary undertaking** and should be the subject of discussion between sponsors and regulators.

Real example

Background (one intercurrent event)

- 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 an RCT 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.

Real example

1. 'Treatment-policy'

A. The *population* is defined through appropriate inclusion/exclusion criteria to reflect the targeted patient population;
B. The *variable* is the change from baseline in weight/functioning after 12 weeks;
C. The *intervention effect* **is regardless of death;**
D. The *summary measure* is the difference in variable means.

Real example

2. 'Composite'

A. The *population* is defined through appropriate inclusion/exclusion criteria to reflect the targeted patient population;
B. The *variable* is **binary; alive and with maintenance of weight/functioning after 12 weeks;**
C. The *intervention effect* **is not applicable as the intercurrent event is captured in the variable definition;**
D. The *summary measure* is the difference **in response proportions.**

Real example

3. 'Hypothetical'

A. The *population* is defined through appropriate inclusion/exclusion criteria to reflect the targeted patient population;
B. The *variable* is the change from baseline in weight/functioning after 12 weeks;
C. The *intervention effect* **had patients not died (and continued treatment?, and discontinued treatment?);**
D. The *summary measure* is the difference in variable means.

Real example

4. 'Principal strata'

A. The *population* is **restricted to patients who would survive 12 weeks if treated *with experimental therapy*" … (or "*with either therapy*" depending on the stratum of interest)** targeted patient population defined by the inclusion/exclusion criteria;
B. The *variable* is the change from baseline in weight/functioning after 12 weeks;
C. The *intervention effect* **is not applicable as the intercurrent event is captured in the population definition;**
D. The *summary measure* is the difference in variable means.

Real example

5. 'While on treatment' = 'While alive'

A. The *population* is defined through appropriate inclusion/exclusion criteria to reflect the targeted patient population;
B. The *variable* is the **area under the curve for weight/functioning while being on randomised treatment;**
C. The *intervention effect* **is not applicable as the intercurrent event is captured in the variable definition;**
D. The *summary measure* is the difference in variable means.

Retrospective example

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia

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ABSTRACT

BACKGROUND

Blinatumomab, a bispecific monoclonal antibody construct that enables CD3-positive T cells to recognize and eliminate CD19-positive acute lymphoblastic leukemia (ALL) blasts, was approved for use in patients with relapsed or refractory B-cell precursor ALL on the basis of single-group trials that showed efficacy and manageable toxic effects.

METHODS

In this multi-institutional phase 3 trial, we randomly assigned adults with heavily pretreated B-cell precursor ALL, in a 2:1 ratio, to receive either blinatumomab or standard-of-care chemotherapy. The primary end point was overall survival.

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Clinical context

- Primary objective: does new treatment result in improved overall survival compared to standard of care
- Patients with relapsed or refractory ALL
- Randomised 2-arm study to compare new treatment versus standard of care
- No treatment switching between groups allowed whilst subjects were taking randomised treatment
- Patients achieving complete remission could receive stem cell transplant

Estimand

- Attributes:
  - A: population - patients with relapsed or refractory ALL
  - B: variable – overall survival
  - C: intercurrent event – regardless of stem cell transplant (SCT)
  - D: population-level summary – hazard ratio of overall survival between treatment groups

The estimand is the hazard ratio of overall survival in all patients randomised who are adult patients with relapsed or refractory ALL regardless of whether patients receive a stem cell transplant

Estimation and Sensitivity Analyses

- The primary analysis compared overall survival between treatment groups using a log-rank test stratified by randomisation factors: age, prior salvage therapy and prior stem cell transplant. The hazard ratio with 95% C.I. was estimated using a stratified Cox proportional-hazard regression analysis. Kaplan-Meier methods were used to estimate the median survival time.
- The sensitivity analysis repeated the primary analyses only including subjects who received randomized treatment.
- Under the new framework, the sensitivity analysis is not aligned to the estimand as the subjects included in the sensitivity analysis is no longer all randomised subjects.
- Examples of sensitivity analyses that are aligned to the estimand include:
  - Assessing the assumption of proportional hazards for overall survival in the randomisation factors
  - Assessing the assumption of non-informative censoring
  - Repeating the primary analysis not stratifying by randomisation factors

ICH E9(R1) Table of contents

Summary

- Estimand reflects the ‘scientific question of interest’
- ICH E9(R1) introduces a new framework to formulate a clear and interpretable trial objective, which in turn leads to a targeted trial design, aligned trial conduct, and aligned statistical analyses
- New framework requires early discussions with clinicians, statisticians, regulators and other stakeholders to harmonize trial objectives
- Discussions relating to methods for estimation and sensitivity analysis follow once an estimand(s) is chosen

Useful References (1)

- ICH concept paper (2014) E9(R1): Addendum to Statistical Principles for Clinical Trials on Choosing Appropriate Estimands and Defining Sensitivity Analyses in Clinical Trials
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- A structured approach to choosing estimands and estimators in longitudinal clinical trials. C. H. Mallinckrodt et al. *Pharmaceut. Statist. 2012,* 11 456–461

Useful References (2)

- Missing Data: Turning Guidance Into Action. C. H. Mallinckrodt et al. Statistics in *Biopharmaceutical Research* 2013, Vol. 5, No. 4, 369-382
- Choosing Appropriate Estimands in Clinical Trials. AK Leuchs et al. *DIA Therapeutic Innovation & Regulatory Science*. 2015
- Estimands and their role in clinical trials. M Akacha et al. Biopharmaceutical Report. Biopharmaceutical Section. American Statistical Association. Summer 2015
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- Current Practices in Choosing Estimands and Sensitivity Analyses in Clinical Trials: Results of the ICH E9 Survey. Fletcher et al. *DIA Therapeutic Innovation & Regulatory Science*. 2016
- Estimands: discussion points from the PSI estimands and sensitivity expert group. Phillips et al. Pharmaceutical Statistics. 2016