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Use of Estimands in Target Trial Emulation

Joint HMA/EMA Big Data Steering Group workshop on RWE methods

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With thanks to EMA colleagues Chantal Quinten and Marcia Rueckbeil

Reflection paper on *Use of RWD in NIS to generate RWE*

4.4. Studies with causal objectives

…

The target trial emulation (TTE) framework should be considered *as a strategy that uses existing tools and methods* ***to formalise the design and analysis of NIS using RWD with causal objectives***

…

To increase the coherence between definitions of exposures, endpoints and intercurrent events, ***the estimand framework described in the ICH E9 (R1)*** *Addendum on Estimands and Sensitivity Analysis in Clinical Trials* ***should be considered in the design of the hypothetical trial****, such as the attributes of the estimand, intercurrent events and strategies to manage ICEs.*

Framework to define the research question in an RCT?

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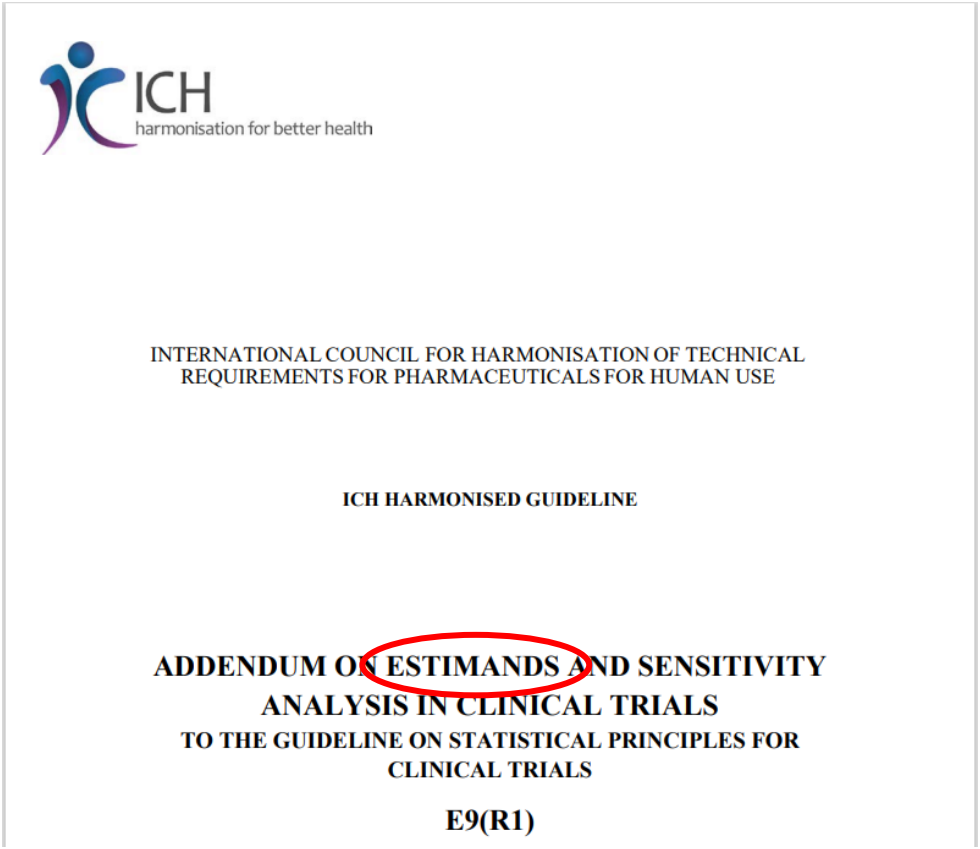


ICH
harmonisation for better health

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

ADDENDUM ON ESTIMANDS AND SENSITIVITY ANALYSIS IN CLINICAL TRIALS
TO THE GUIDELINE ON STATISTICAL PRINCIPLES FOR CLINICAL TRIALS

E9(R1)

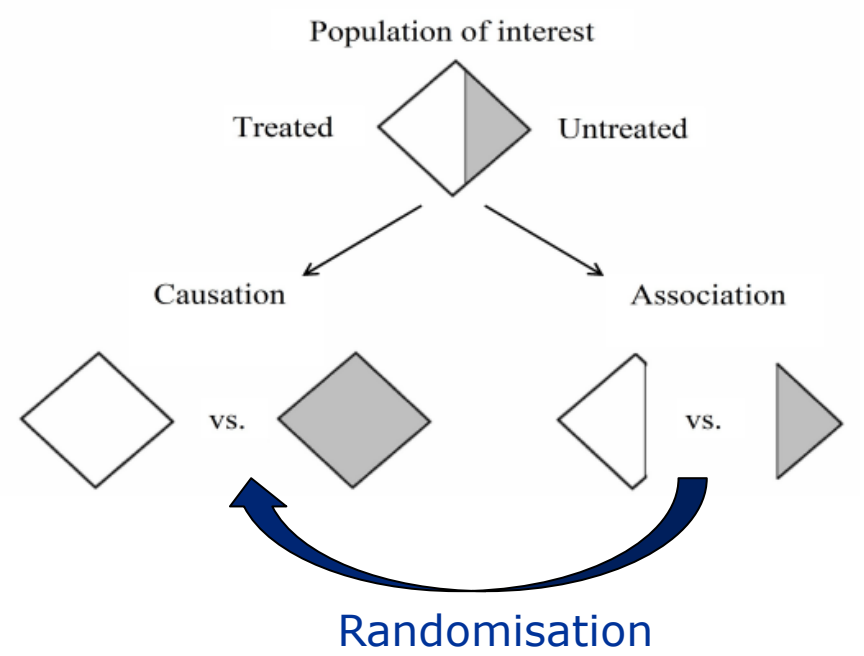
*"An estimand is a **precise description of the treatment effect** reflecting the clinical question posed by a given clinical trial objective."*

ICH E9(R1) is driven by causal inference principles

Definition of treatment effect in guideline:

A.3. ESTIMANDS
[…] treatment effects: how the outcome of treatment compares to what would have happened to the **same subjects** under alternative treatment (i.e. had they not received the treatment, or had they received a different treatment).

Fig 1.1 from Hernán and Robins (2020)



ICH E9(R1) addressed other gaps and lack of clarity in RCTs

- Lack of logical connectivity between trial objectives, design, conduct, analysis and interpretation
- Missing data: *"Data that would be meaningful for the analysis of a given estimand but were not collected. They should be distinguished from data that do not exist or data that are not considered meaningful because of an intercurrent event."*
  - Treatment discontinuation -> to be addressed in the estimand
  - Study withdrawal -> missing data to be addressed in the estimation method
- Clarification of the role of "sensitivity analysis": analysis to address the robustness of the results to departures from assumptions made in the primary analysis

ICH E9(R1) in a nutshell

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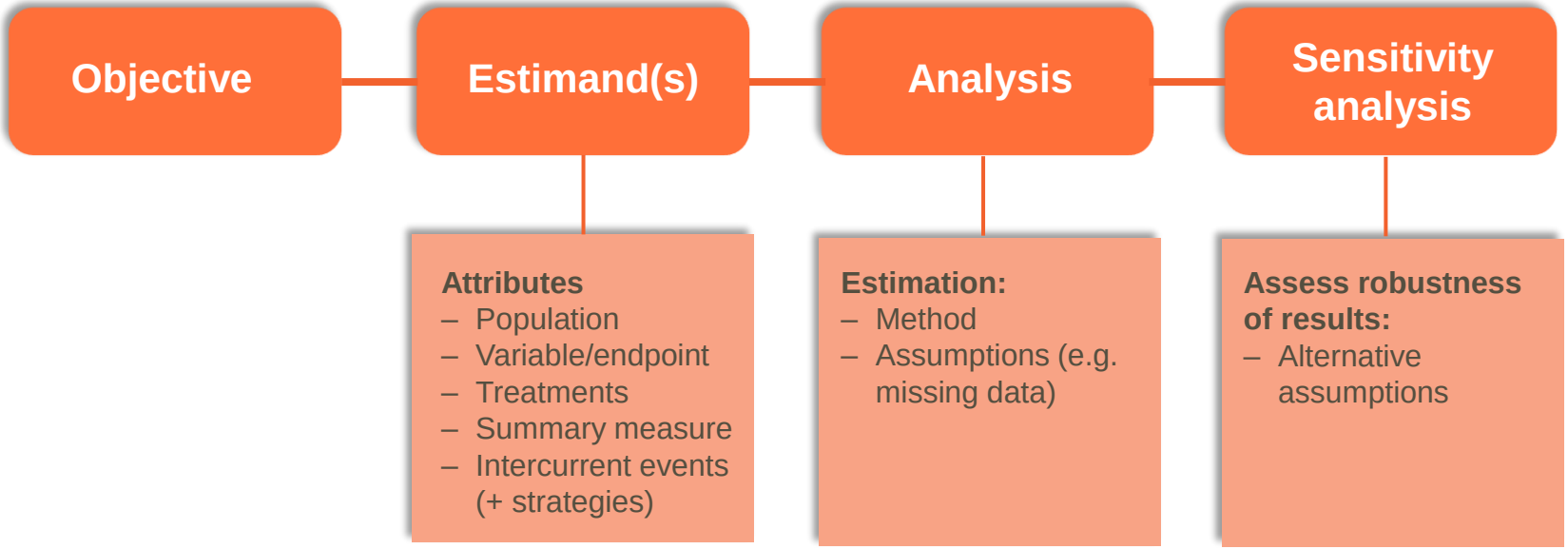
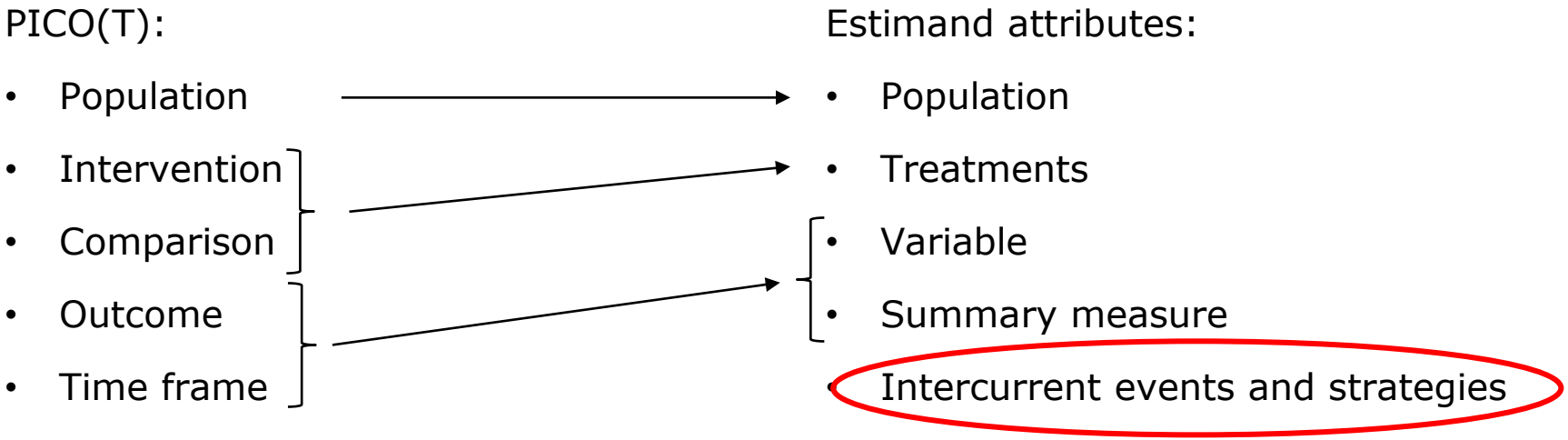
Four key elements that must be aligned



Estimands vs PICO(T)

- Causal inference principles shared between Estimands and PICO(T) frameworks



- One can think of Estimands as an evolution of PICO(T)

Based on a true story

(Example for illustrative purposes inspired in ICH E9(R1) training materials)

In the past, one could find something like this in the study protocol of an RCT:

- Objective: To investigate the efficacy and safety of dapagliflozin for the treatment of type II diabetes mellitus compared to 'control'
- Primary endpoint: Change in glycated haemoglobin (HbA1c) from baseline to week 24
- Analysis method: The primary endpoint will be analysed using an Analysis of Covariance (ANCOVA) model with terms for treatment and baseline HbA1c

The PICO(T) elements can be identified from the above:

- Population: patients with type II diabetes
- Intervention: dapagliflozin
- Control: some 'control' treatment
- Outcome: Change from baseline in HbA1c
- Time frame: Week 24 after initiation of treatment

Based on a true story…

(Example for illustrative purposes inspired in ICH E9(R1) training materials)

While assessing the evidence submitted in the MAA

- Applicant: *"Data collected after initiation of rescue medication were excluded from the analysis."* (Single imputation used with last observation carried forward.)

Treatment effect: **dapagliflozin** vs **control** in the absence of rescue medication

- Regulator: (Disagreed with the exclusion of data post-rescue medication) *"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."*

Treatment effect: **dapagliflozin** vs **control** regardless of use of rescue medication

Why the misunderstanding?

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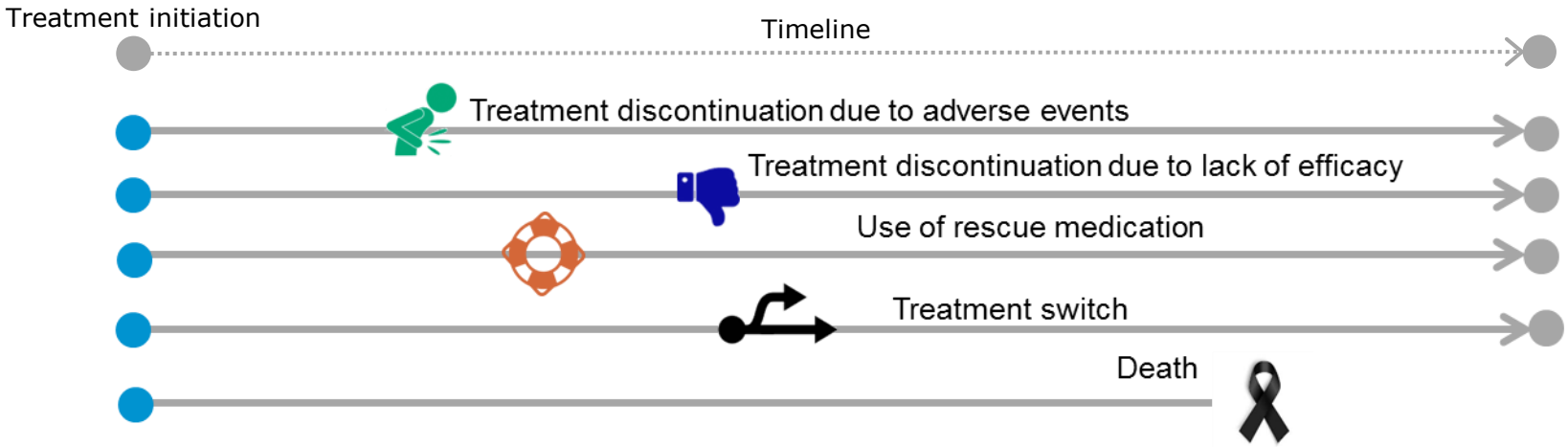
- PICO(T) elements agreed by applicant and regulator
- And yet, applicant and regulator understood different things
  - Applicant:
    Treatment effect: **dapagliflozin** vs **control** in the absence of rescue medication
  - Regulator:
    Treatment effect: **dapagliflozin** vs **control** regardless of use of rescue medication
    (i.e. *dapagliflozin+rescue* vs *control+rescue*)
- These are two different treatment effects, which are appropriately thought of as **different questions (estimands)** and not two different answers to the same question
- What was missing? The identification of the **intercurrent event** "use of rescue medication" and a strategy to handle it (A: "hypothetical", R:"Treatment policy")
- This discussion should happen at the design stage, not at the analysis stage

Intercurrent events

Intercurrent events:

"Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest."

Examples of intercurrent events:



We cannot identify upfront who will experience IEs -> observational nature

Strategies for handling intercurrent events

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Intercurrent events:

"Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest."

Strategies for handling intercurrent events

- **Treatment policy**. Treatment effect regardless of the occurrence of the IE
- **Hypothetical**. Treatment effect in a hypothetical world where the IE would not occur
- **Composite**. Treatment effect considering IE as a bad health outcome on its own
- **While-on-treatment**. Treatment effect before the IE occurs
- **Principal Stratum**. Treatment effect in the stratum of subjects who would (not) experience the IE (not to be confused with the subgroup of subjects who did)

Target Trial 'causal contrast (ITT, PP)' revisited

- Estimand framework diminished role of PP and expanded strategies for ITT principle
- Remember one of the suggested key elements of the target trial to be specified:
  - Eligibility criteria
  - Treatment strategies
  - Assignment procedures
  - Follow-up period
  - Outcome
  - **Causal contrasts of interest (ITT, PP)**
  - Analysis plan

Identify IE and then choose strategy:
- Treatment policy
- Hypothetical
- Composite
- While on treatment
- Principal stratum

ICH E9(R1): challenging to identify an estimand to which PP would align

Example – Immunotherapies to treat NSCLC

NIS to investigate effectiveness of selected immunotherapies to treat locally advanced or metastatic non-small cell lung cancer (NSCLC).

Estimand attributes

Population: Patients with locally advanced or metastatic NSCLC

Treatments: Pembrolizumab, Nivolumab, Atezolizumab, Cemiplimab, Durvalumab, Ipilimumab, Chemotherapies (control), given as first line of treatment

Variable: Overall survival from therapy start

Summary measure: The hazard ratio will be used for comparison between immunotherapy and chemotherapy treatment groups

Intercurrent events:treatment discontinuation and treatment switch. Both dealt with a treatment policy strategy

Estimand description
(Research question of interest)

Estimand: what is hazard ratio of time to death from any cause in selected immunotherapies given as first line of treatment compared to chemotherapies given as first line of treatment regardless of treatment discontinuation or switch?

An additional estimand is considered by changing the summary measure to "difference in RMST"

Discussion

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- PICO(T) framework used to define the research question in NIS. Also used in new legislation for joint European Health Technology Assessment (EU HTA)
- Estimands framework used to define clearly the research question addressed with an RCT. Estimands must be specified in study protocols of RCTs
- Target Trial Emulation offers a bridge between RCT and NIS
- Use of the estimands framework to define the target trial will make the bridge more robust by adding clarity on RCT elements to be emulated
- Consideration to other elements of ICH E9(R1) would also be beneficial
  - Estimands and estimation are separate discussions
  - Changes in estimand attributes lead to different estimands, not to sensitivity analyses
  - Set the estimand, then choose the estimation method and then consider sensitivity analyses to assess the robustness of the results to assumptions made in the estimation method

Any questions?

Further information

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