An Introduction to Estimands – Tell me what you want. What you really, really want.

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October 27, 2023 – Basel Epidemiology Seminar. RWD Frameworks: Estimands, Target Trial Framework.

Disclaimer

The views and opinions expressed in this presentation are solely mine and not necessarily those of my employer.

Reporting treatment effects for a cancer study

- Study to evaluate the effect of a treatment on preventing disease progression and death
- Quality of life change from baseline analyzed with a mixed ANCOVA linear repeated measures model

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A. expected to be in a hypothetical setting where patients never experience disease progression / death

B. at the end of the study in those patients who did not experience disease progression or died

C. at the last point in time before patients experienced disease progression or died

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Estimand – Definitions

Estimand (Latin: aestimandum) = 'that which is being estimated'

Roos CF, von Szeliski V (1939): JASA.
Mosteller F, Tukey JW (1968): Handbook of Social Psychology: Research Methods.

Inference focuses on summaries of these measures (such as the mean) for the target population of interest. These summary quantities are often called parameters, or estimands.

[National Research Council (2010). The Prevention and Treatment of Missing Data in Clinical Trials.]

We refer to the parameter of interest in the super-population [= target population] as the estimand.

[Hernán MA, Robins JM (2020). Causal Inference: What If. Boca Raton: Chapman & Hall/CRC.]

Estimand:
A precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarises at a population-level what the outcomes would be in the same patients under different treatment conditions being compared.

ICH E9(R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials, 2019.

Defining the treatment effect reflecting the clinical question

ICH E9(R1)

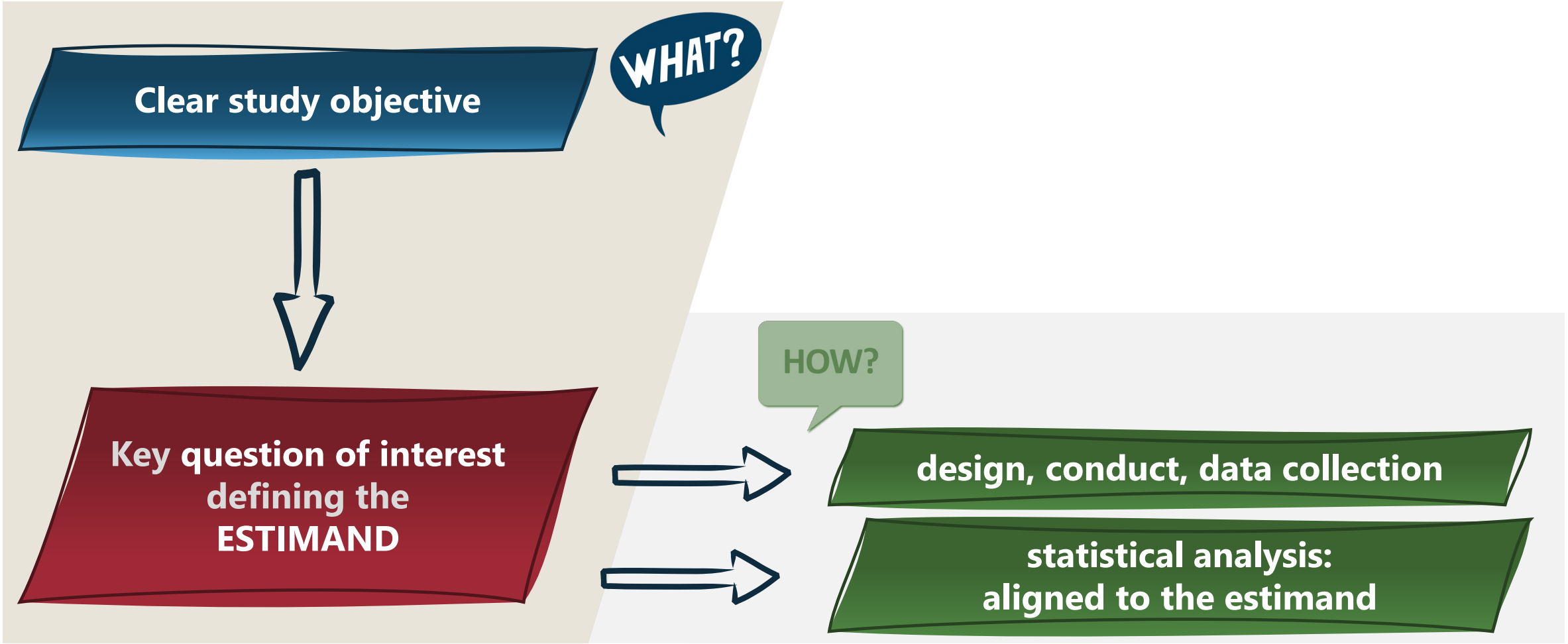
PURPOSE

- provide **clear descriptions** of the benefits and risks of a treatment
- support researchers in precisely and transparently **specifying the treatment effect** they **aim** to estimate

SCOPE

- principles of the **estimand framework** are
  - relevant whenever a treatment effect is estimated (efficacy or safety)
  - applicable for randomized clinical trials, single arm trials, and observational studies

A systematic approach to thinking through study objectives



The treatment effect of interest clearly spelled out

ICH E9(R1)

Target population

Individuals targeted by the clinical question

Treatment

Treatment condition (+ treatment to which comparison is made)

Endpoint / variable

Measure(s) for each individuum to address a clinical question

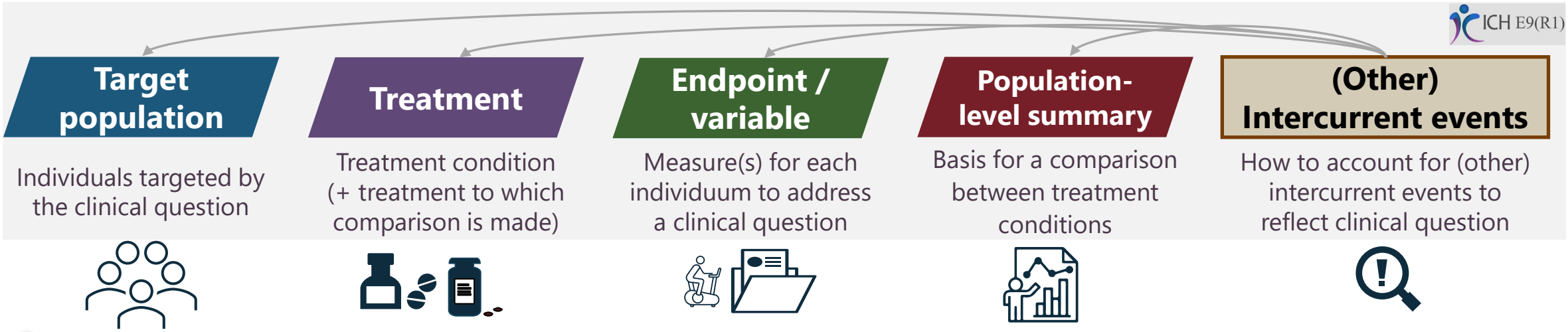
Population-level summary

Basis for a comparison between treatment conditions

(Other) Intercurrent events

How to account for (other) intercurrent events to reflect clinical question

The treatment effect of interest clearly spelled out



The study will compare <test treatment condition> with <reference treatment condition> in individuals who <target population>.

The objective is to <*desired goal/claim**> based on the <population-level summary measure> for the <endpoint/variable>.

The treatment effect of interest is <high-level description of accounting for *other* intercurrent events>.

**eg* 'show superiority'

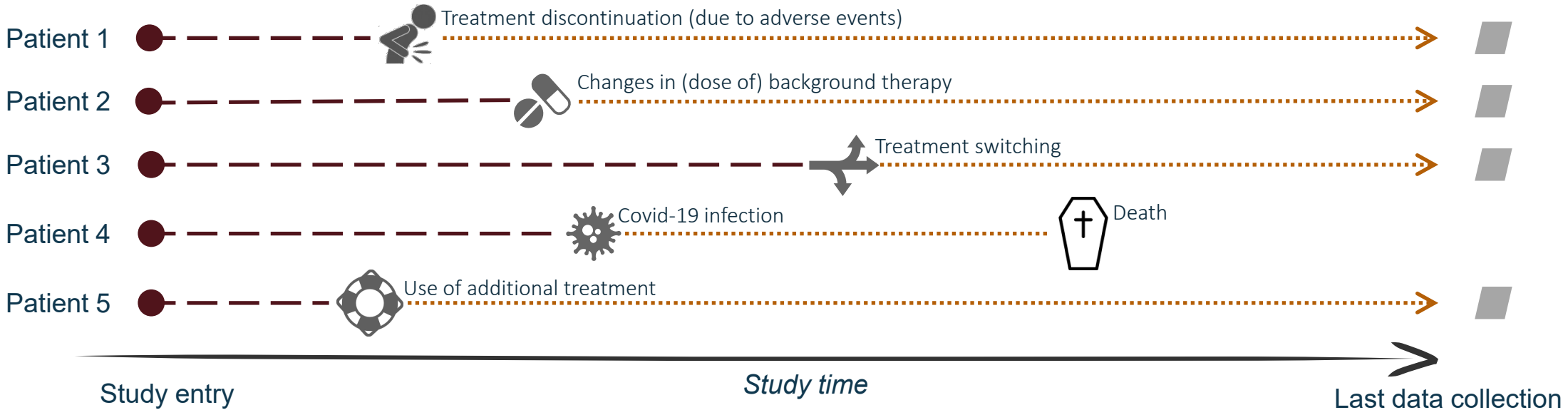
Detailed clinical objective template from Bell J, Hamilton A, et al. The detailed clinical objectives approach to designing clinical trials and choosing estimands. Pharmaceutical Statistics. 2021;1–13

Diversity in patient journeys

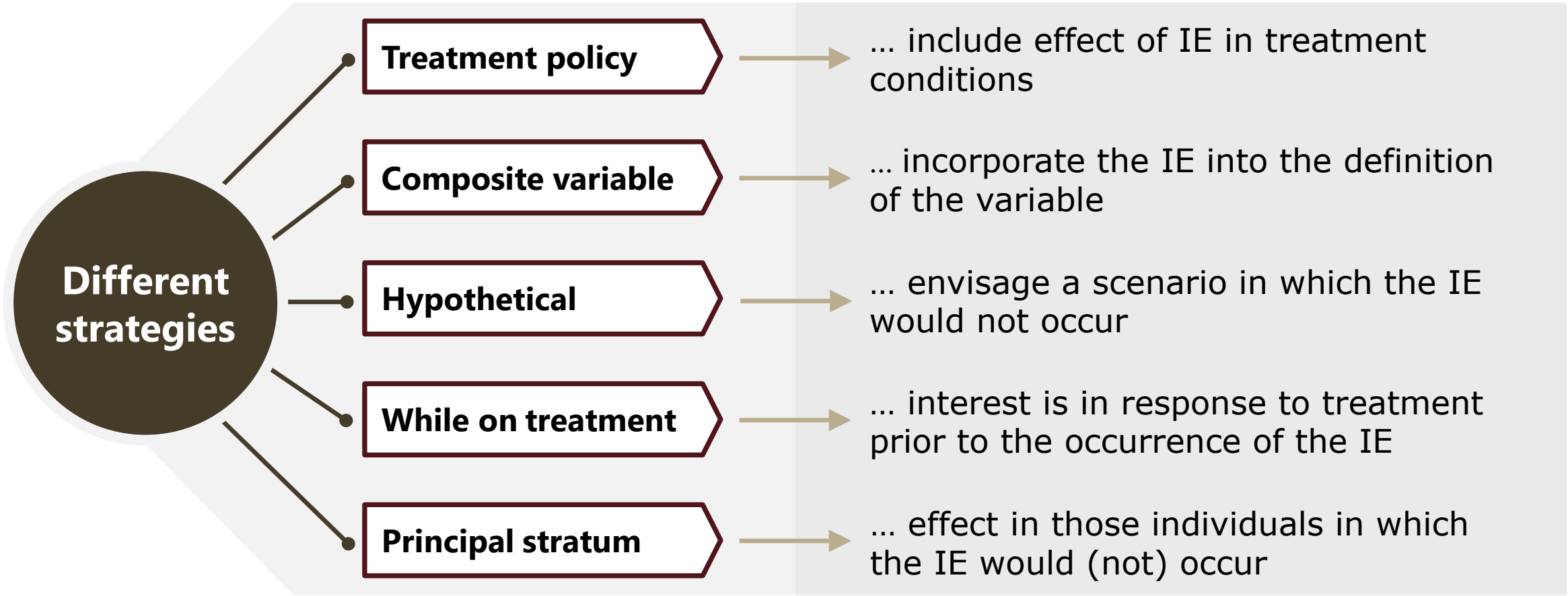
ICH E9(R1)

Intercurrent events…

- occur after treatment initiation (or prescription)
- affect either the interpretation or the existence of data associated with the question of interest



How to address intercurrent events (IEs)



Estimands and PICO(TS) to precisely state the clinical questions

ESTIMAND

ICH E9(R1)

Target population	Treatment	Endpoint / variable	Population-level summary	(Other) Intercurrent events
Individuals targeted by the clinical question	Treatment condition (+ treatment to which comparison is made)	Measure(s) for each individuum to address a clinical question	Basis for a comparison between treatment conditions	How to account for (other) intercurrent events to reflect clinical question





Patient Population	Intervention Comparator		Outcome	Time	Setting
P	I	C	O	T	S
Group of participants to be studied	Treatment to be studied+ Intervention for comparison		Measurable change in individuum's health status	Duration of the study	Location of the study


Richardson, S., Wilson, M. C., Nishikawa, J., & Hayward, R. S. (1995). The well-built clinical question: a key to evidence-based decisions. *ACP journal club*, *123*(3), A12-13.

Target Trial Emulation

1. Articulate a meaningful, well-defined **causal question**.

   Imagine the **hypothetical randomized trial** that could be designed to address this question.

   Specify in protocol: eligibility criteria, treatment strategies, treatment assignment, start/end of follow-up, outcome definitions, causal contrasts, analysis plan

2. Explicitly emulate the components of this protocol using observational / RW data
   - find eligible individuals
   - assign them to a treatment strategy compatible with their data
   - follow them up from assignment (time zero) until outcome or end of follow-up
   - conduct the same analysis as the corresponding target trial, but adjust for baseline confounders in an attempt to emulate random treatment assignment

Hernán MA, Wang W, Leaf DE. Target Trial Emulation: A Framework for Causal Inference From Observational Data. JAMA. 2022;328(24):2446–2447. doi:10.1001/jama.2022.21383

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Thank you!

Contact

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