A (short) introduction to estimands

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Statistical Advisory Services

Part of the activity of the section of biostatistics is to advise health researchers in carrying out medical studies.

A key task is to ensure a good alignment between:

- the research question.
- the study design.
- the analytical tools (e.g. statistical models & tests).
- the interpretation of the results.

The **estimand framework** is frequently used at the section to facilitate the discussion between experts from different domains (e.g. statisticians and medical doctors).

- it is also the recommended way to perform the biostatistical analysis according to clinical trial guidelines,
  e.g. ICH E9 addendum on estimands (2020)

What is an estimand?

Definition (Oberndorfer et al., 2026)

Estimands represent the quantities of interest that a study sets out to estimate

- they translate a study's research questions into specifically targeted estimates that try to answer these questions

Illustration (Oberndorfer et al., 2026)

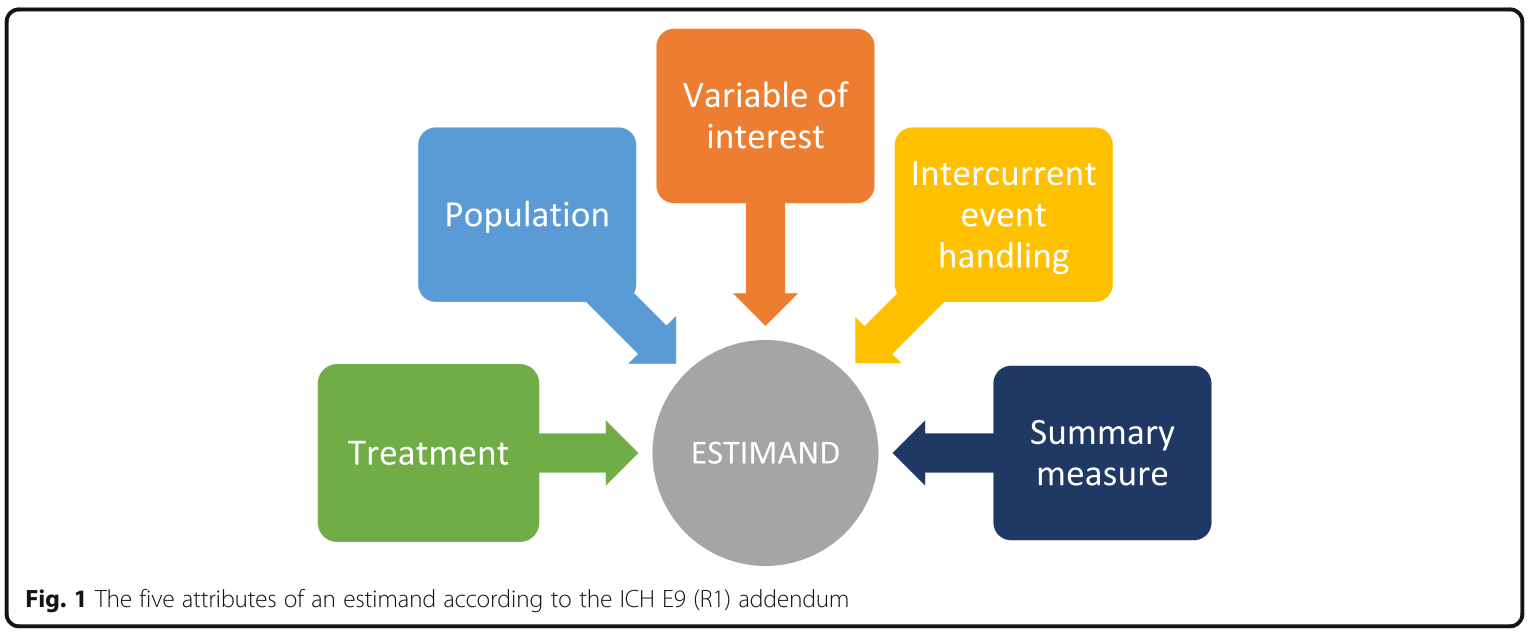
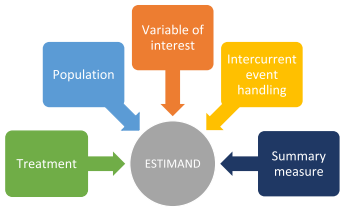


Fig. 1 The five attributes of an estimand according to the ICH E9 (R1) addendum

Example - inspired from Hansen et al. (2025)

Research question: comparing the efficacy of two mRNA vaccine (A vs. B) against Covid-19 disease?

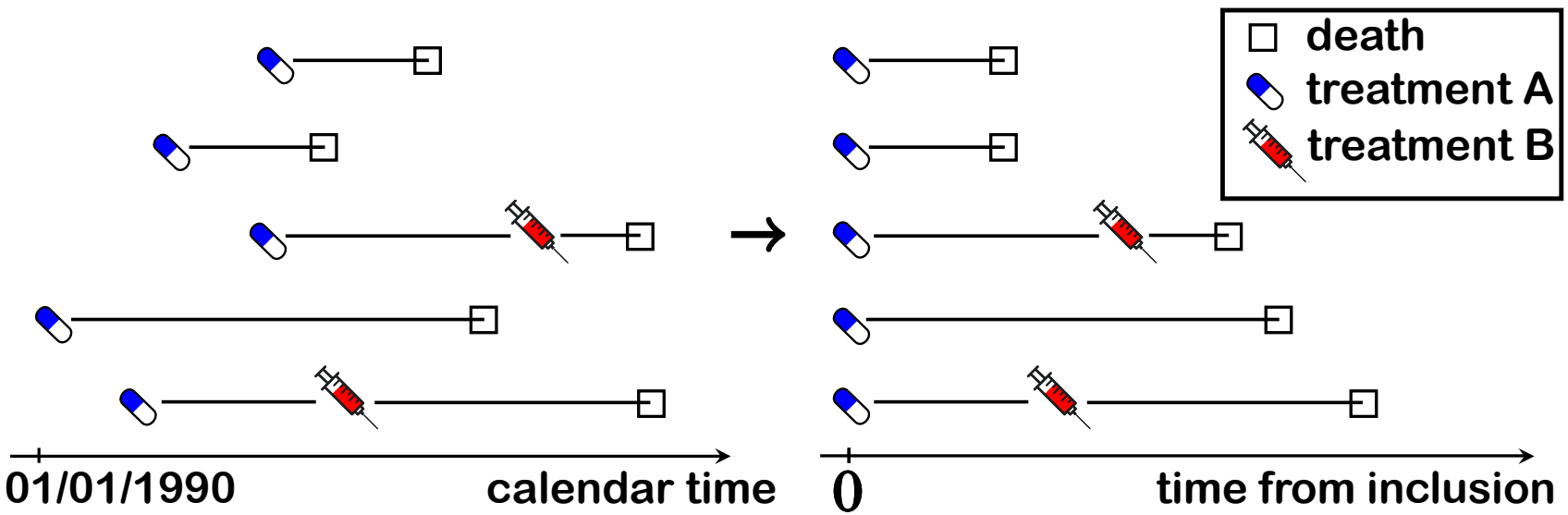


Estimand (intention to treat):

In the danish population of 65 years and older in 2021, what is the difference in proportion of patients being hospitalized with COVID-19 as primary reason for admission from 14 days after randomization up to 6 months between the group of patients offered two doses of A compared to one dose of B regardless to adherence to the scheduled dose or switch to another vaccine.

'Confusing' example with observational data

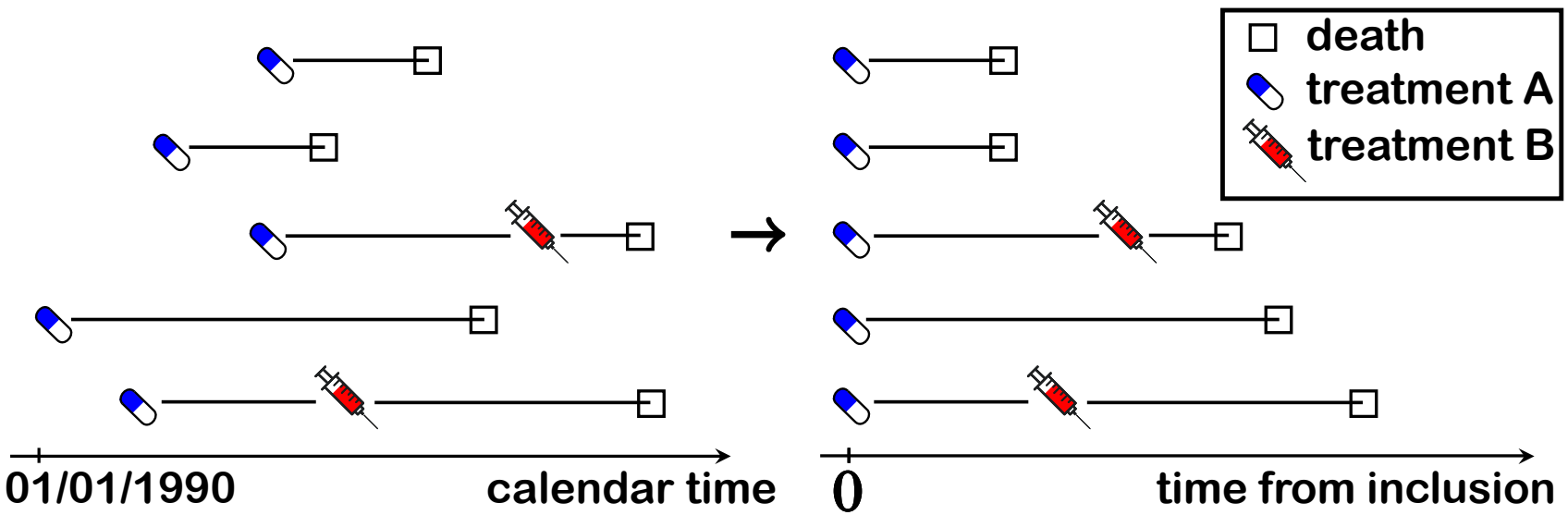
- **Research question:** comparing the survival of patients who switch treatment vs. who stayed on treatment



- **Estimand:**

'Confusing' example with observational data

- **Research question:** comparing the survival of patients who switch treatment vs. who stayed on treatment



- **Estimand:** 😱 what is meant by switching treatment?
  - switching after a 'fixed' time (e.g. 2-3 months)
  - switching if initial drug seems ineffective
  - switching if recovery

Why estimands?

Clarify the intent of the study to the reader

Oberndorfer et al. (2026): Be upfront about the research study's intention [. . .] - is it to describe, predict, or estimate causal effects (these are all very different tasks).

What is (descriptive/association) vs. what if (causal)

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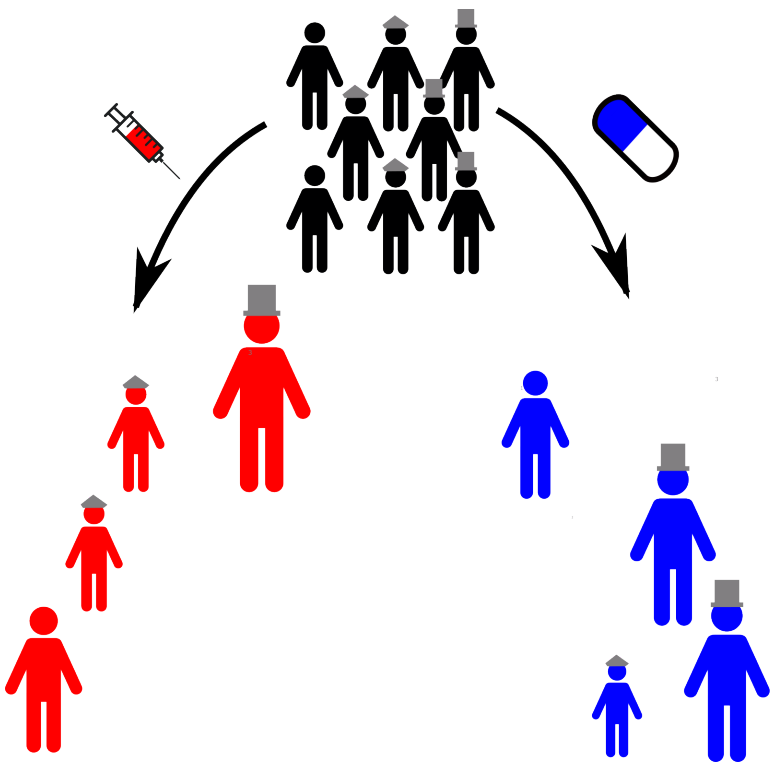

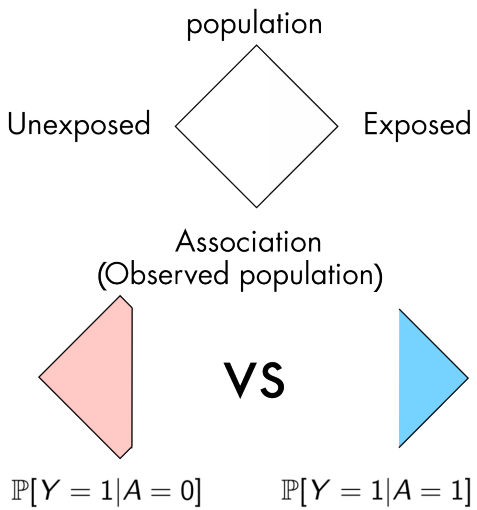

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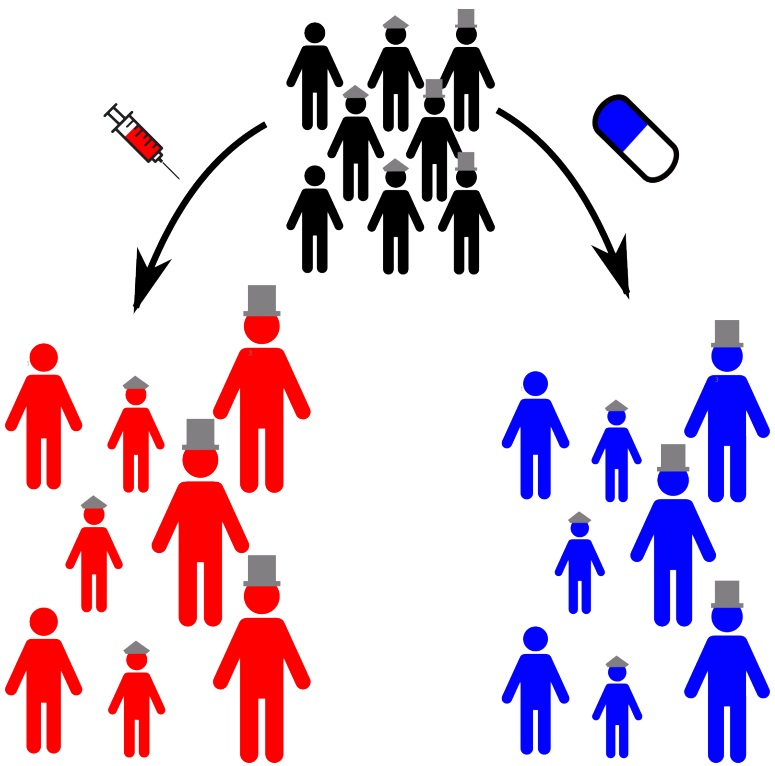
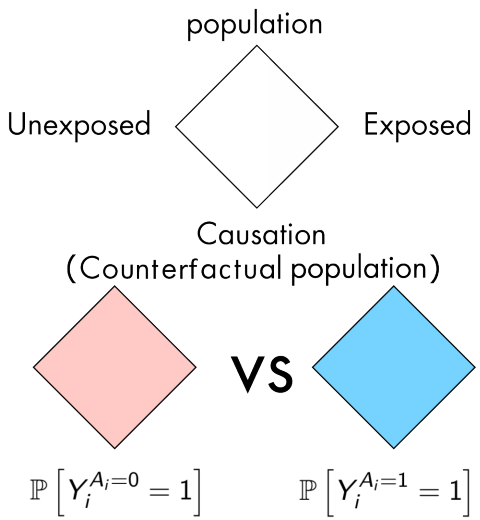




What are intercurrent events?

Definition (Kahan et al., 2024)

Intercurrent events are post-baseline events (or postrandomisation events in randomised trials) that affect either the interpretation or existence of outcome data.

- these generally fall into two distinct categories: treatment-modifying events and truncating events.

Examples

- treatment discontinuation due to an adverse event
- start of a rescue medication
- pregnancy (in a study about contraception)
- death, miscarriage (if outcome is neonatal birth weight)

How to handle intercurrent events? Kahan et al. (2024)

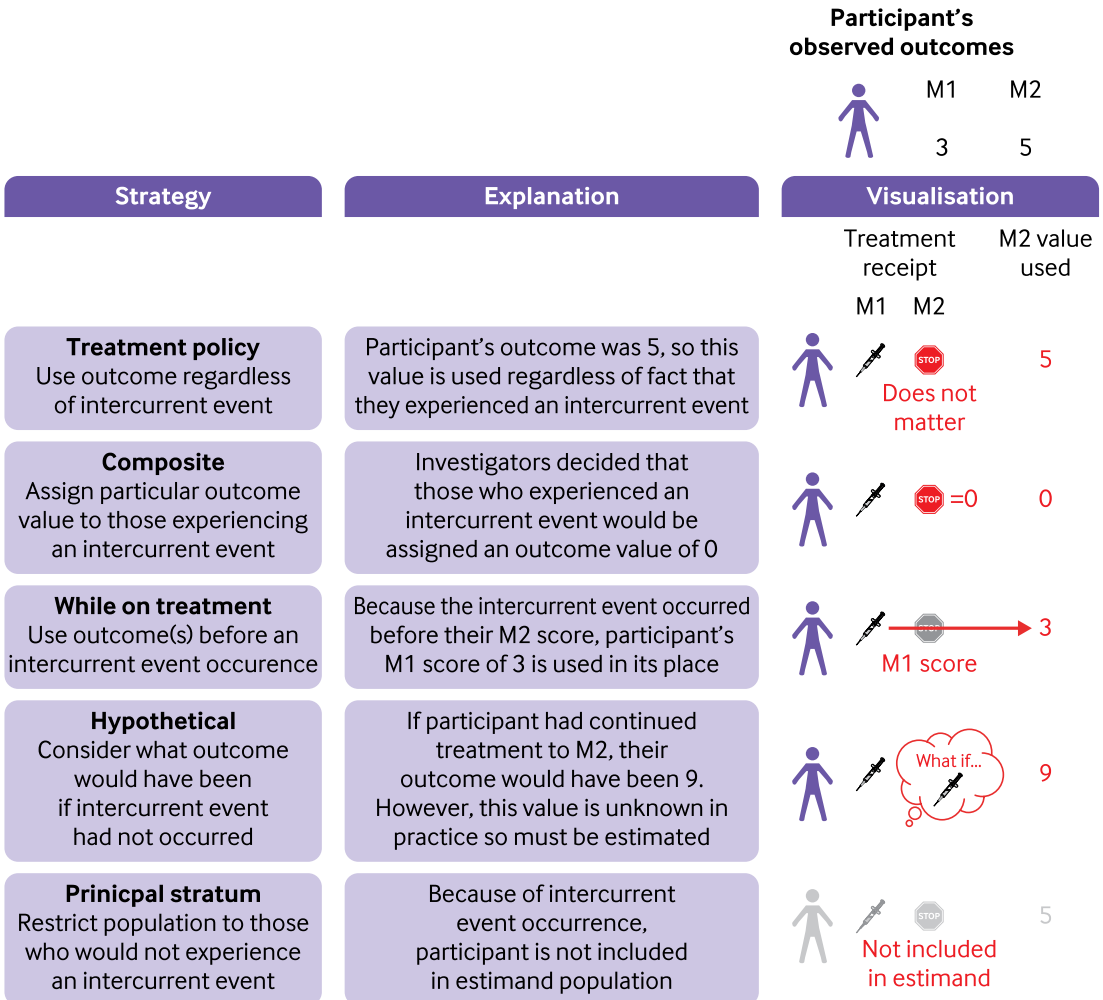
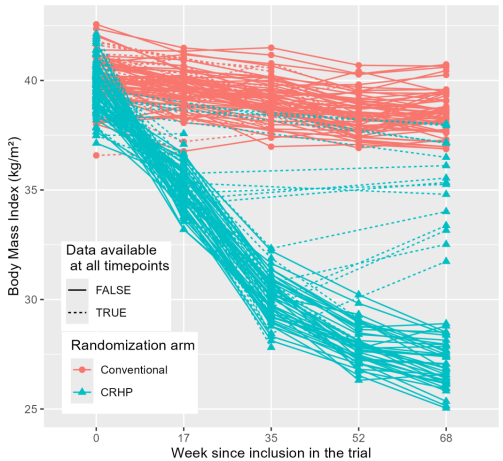


Fig 1 | Different strategies regarding intercurrent events. In this example, a randomised trial compares intervention with control to understand how outcomes differ at month 2. However, one participant stops treatment before month 2 (ie, an intercurrent event). The figure shows what happens to this participant under each intercurrent event strategy. Under a composite strategy, investigators have decided to assign a score of 0 to any participant who experienced an intercurrent event. Under a while-on-treatment strategy, because the participant experienced an intercurrent event before month 2, their month 1 score of 3 is used in place of their month 2 score. Under a hypothetical strategy, the participant's outcome that would have occurred had they continued treatment at month 2 is used (here, it is a value of 9); but in practice, this value will not be known and so must be estimated. M=month

Consulting case - inspired from Kopp et al. (2024)

A collaborator asks for your advise on what analysis to pre-register for her weight-loss trial.

She articulates the **research question** as: 'compare the effect of a conventional vs. carbohydrate-reduce high-protein diets on weight loss among individuals with type 2 diabetes and high BMI'.



Your task as statistical consultant is to:

- provide **recommendations** to the collaborator
- **prepare questions**. Questions can be clarifying questions or about extra information you would need from your collaborator.

Reference I

Hansen, C. H., Lassaunière, R., Rasmussen, M., Moustsen-Helms, I. R., and Valentiner-Branth, P. (2025). Effectiveness of the bnt162b2 and mrna-1273 jn. 1-adapted vaccines against covid-19-associated hospitalisation and death: a danish, nationwide, register-based, cohort study. *The Lancet Infectious Diseases*, 25(12):1293–1302.

ICH E9 addendum on estimands (2020). Ich e9(r1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials. Scientific Guideline EMA/CHMP/ICH/436221/2017, European Medicines Agency, Amsterdam, Netherlands. Adopted at Step 5.

Kahan, B. C., Hindley, J., Edwards, M., Cro, S., and Morris, T. P. (2024). The estimands framework: a primer on the ich e9 (r1) addendum. *bmj*, 384.

Reference II

Kopp, L. H., Søgaard-Hansen, C. M., Zachhau, K. M., Bastkjær, R. M., Andersen, B. V., Budtz-Jørgensen, E., Byrne, D. V., Chaaban, N., Holst, J. J., Klindt, T. B., et al. (2024). Effects of a carbohydrate-reduced high-protein diet delivered with meal kits to danish people with type 2 diabetes: protocol for a 12-month randomised controlled trial. *BMJ open*, 14(8):e084686.

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