Estimands Key theme Stratos, future plans

Within the week four different subprojects emerged on which we could work further after the Lorentz workshop:

1. Estimands in illness death models
2. Unifying different estimand frameworks
3. Extend estimand thinking beyond causality
4. Sensible estimands

A short description per project

1. Different estimands in illness death models

This project is inspired by the talk of Malka Gofiner, who discussed seleveral estimands for illness-death models. (cfr. Nevo, D. and Gorfine, M. (2022). Causal inference for semi-competing risks data. Biostatistics, 23(4):1115–1132.)

a. Leaders: Pamela Shaw and Els Goetghebeur
b. Participants: Pamela Shaw, Malka Gorfine, Maja Pohar Perme, Hein Putter, Dries, Reynolds, Terry Therneau, Els Goetghebeur (full author list and order TBD)
c. Topic groups involved: TG7, TG8 and TG4 (?)

Plan: we will discuss criteria for an estimand to satisfy in order to be useful in the biomedical context. We then provide a critical review of several estimands proposed for the illness-death setting and use these criteria to evaluate their potential to provide meaningful assessment of an effect of exposure or treatment that could in turn be informative to clinical decision making or scientific discovery. Beyond examining the meaning and usefulness of these estimands we will also consider the critical assumptions needed for their identification from data (and how they can be estimated).

We will illustrate application of these principles using data from a case study that considers `the effect of the APOE e4 gene' on Alzheimer's disease and death.

Targeted audience for this paper are applied statisticians and those needing to also interact with clinicians (level 2), as well as statistical methodologists who seek to develop estimands that can be more readily and more reliably put into practice in order to inform clinical decision making by real world data. This paper has links with the topic of Sensible Estimands.

Next steps:

- Identify who else wants to join this project, and consider possible links with the Sensible Estimands project
- Discuss the provisional paper outline between Pam, Malka and Els
- Get together online with the interested people.

2. Different estimand frameworks

This project is targeting those who start conducting causal research and are overwhelmed by the different estimand frameworks for treatment effects. Also it is meant to make people who already know one of the estimand frameworks, familiar with the others.

a. Leaders: Saskia le Cessie, Nan van Geloven, Nicholas Bakewell, …. (this may change if there are any other volunteers who want to pick it up.
b. Potential participans:
    a. Saskia le Cessie
    b. Nan van Geloven
    c. Doranne Thomassen
    d. Kelly van Lancker
    e. Nicholas Bakewell
    f. Jonathan Bartlett
    g. Suzanne Cadarette
    h. Emmanuelle Boutmy (?)
    i. Pamela Shaw (?)

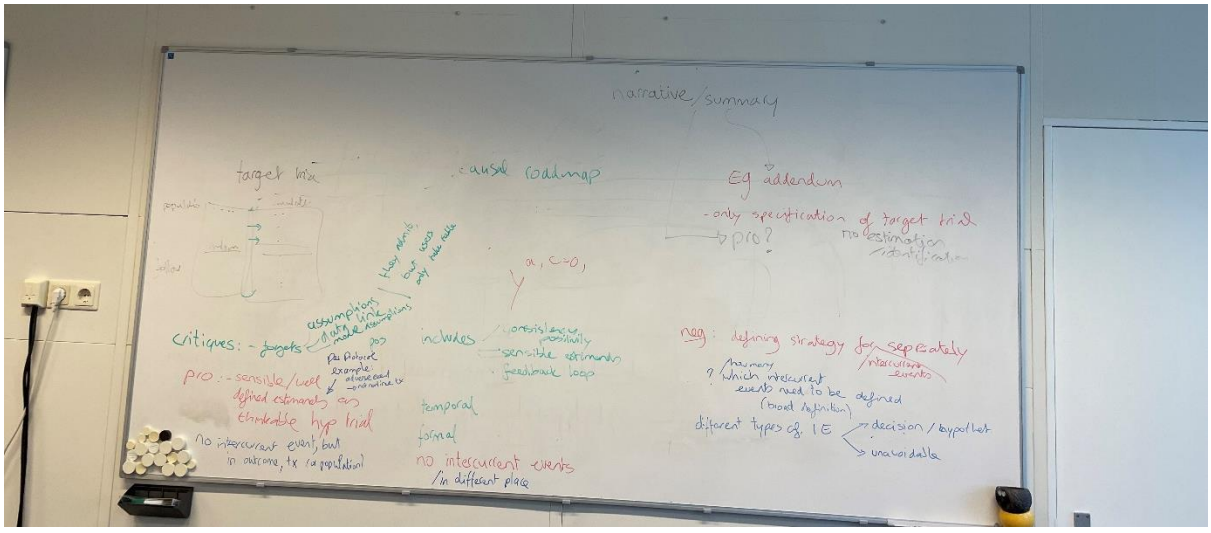
c. Topic groups involved: TG7, TG5, TG1

Plans
We aim to consider the following frameworks:

1. ICH-E9 addendum on estimands
2. Target trial emulation
3. Causal Roadmap
4. The 7 steps described at the tutorial paper of TG 7 (Goetgebeur et al Stat in Med 2020).

The first discussions took place at the Lorentz center. Remarks being made were

- Intended level is level 1.
- We aim to make a large table with different items of the frameworks side to side, connecting what they have in common and pointing our omissions if any.



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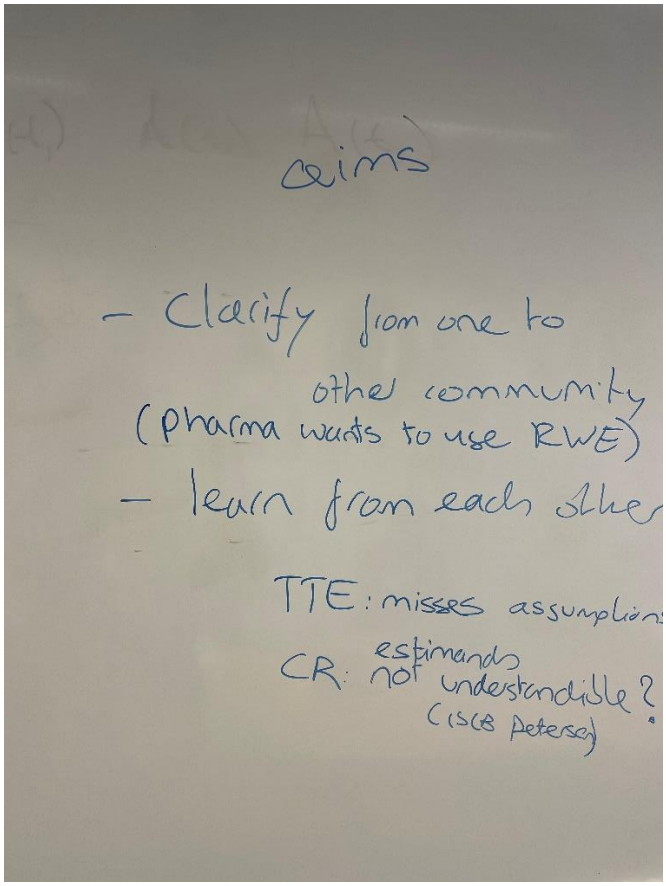

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- Target trials are overused. It is now used as a quality mark for conducting observational reserach, while some studies are not well conducted (definition time zero), or no attention has been placed on the assumptions needed to emulate the target trial.
- Target trials do not explicitely state the underlying identyfiability assumptions.
- The causal roadmap accounts for iterations between identifyability assumptions and the definition of the estimand. The other frameworks are less explicite about it.
- The ICH-E9 estimand framework stops at the definition of the estimand, and does not connect it directly to the analysis (i.e. a treatment policy does not make sense if the follow-up of patients stopts after treatment discontinuation), although it is stated that collecting of the data and the analysis should match the estimand.
- We noted that estimands should be “feasible”, that means under sensible assumptions estimable with the data, and not over-ambitious.
- In trials only specifying design and analysis was deemed insufficient, this motivated ICHE9 framework. In target trial specification we also ‘only’ specify design and anlaysis. Intercurrent events are not an element in the usual tables. Intercurrent events are sometimes translated into description of ‘perfect’ follow up.

At the meeting I was approached both by Frank Harell and by Marc Vandemeulebroecke, who both indicated that there is quite some critique from practicioners that the ICH-E9 estimand framework is very difficult to work with in practice. So this is a point which may also be addressed.

After the meeting Nicolas mailed us with extra information. A list with literature is put on dropbox. In particular the commentary on the Target Trial Emulation Framework that appeared in the journal

Epidemiology in 2023/4, which included some (current/past) STRATOS members, as it is a nice read and provides a few perspectives and highly recommend the following article: Process guide for inferential studies using healthcare data from routine clinical practice to evaluate causal effects of drugs (PRINCIPLED): considerations from the FDA Sentinel Innovation Center, which could motivate our overview/provide some inspiration. However, it is heavily biased towards the Target Trial Emulation framework (which makes sense given the list of authors).

Next steps:

1. Send this report around and ask who else would be interested
2. set up a meeting to discuss plans.

3. Extend estimand thinking beyond causality

Many people associate estimands with causal reasoning, but thinking in estimands may go beyond standard causal inference .

a. Leaders: Saskia le Cessie, Nan van Geloven (this may change if there are any other volunteers who want to pick it up , maybe Ben van Calsteren , Laure Wynants).
b. Potential participans:
    a. Saskia le Cessie
    b. Nan van Geloven
    c. Ben van Calsteren
    d. Laure Wynants
    e. Doranne Thomassen
    f. Kelly van Lancker
    g. Nicholas Bakewell
    h. Suzanne Cadarette

c. Nan asked Ben van Calsteren and Laure Wynants and they also expressed their interest, specifically for estimands in diagnostic research.
d. Topic groups involved: TG7, TG5, TG1, TG 6.

An example of estimand thinking in prediction reserach is the paper of Van Geloven et al (Eur J Epidemiol, 2020), where the role of treatment as intercurrent event is being discussed. Another example in descriptive context is the paper of Thomassen et al (submitted to BMC meth in med), where the ICH-E9 framework is used in a single arm study with a descriptive aim. In the diagnostic research there is often challenge of missing index or reference tests, where choices have to be made on whether and how to impute. Ben and Laure have case studies in this. Also in this diagnostic context we think that thinking in estimands may provide clarity. In general we would like to extend the estimand framework to 3 areas:

a. Prediction
b. Diagnostic
c. Descriptive

In all fields it is important to define a target population and an outcome and in all fields there may be intercurrent events which may interfere with the outcome of interest . We may look at the relation between estimands and the Critical Appraisal tools in Evidence-Based medicine: https://www.cebm.ox.ac.uk/resources/ebm-tools/critical-appraisal-tools

Intended level is level 1

Next steps

Ben and Laure will discuss the topic with Ewout and Patrick Bossuyt (TG6).

4. Sensible estimands

Many new estimands are being proposed by statisticians working on clinical trials and observational studies within the causal inference framework. Some of these estimands have a rather complex interpretation or can only be estimated under unrealistic assumptions. A recent paper of Vansteelandt and Van Lancker https://arxiv.org/abs/2409.11162 discusses estimands with unrealistic assumptions.

a. Leaders: Kelly Van Lancker plus ??
b. Potential participans:
    a. Saskia le Cessie
    b. Nan van Geloven
    c. Doranne Thomassen
    d. Pam Shaw
    e. Els Goetghebeur
    f. Nicholas Bakewell
    g. Jonathan Bartlett
    h. Suzanne Cadarette
    i. Veronika Deffner (?)
    j. Emmanuelle Boutmy (?)
    k. Stijn Vansteelandt

c. Topic groups involved: TG7, TG5, TG1.

In a discussion meeting, we discussed that

- Many estimands are not very useful in practice, such as a hypothetical estimand in QOL for end-stage cancer in a world where people not die, or estimands which are very difficult to understand such as “The strength-of-IV weighted average treatment effect” .
- Unrealistic assumptions may be another issue. Assumptions should be reasonable. We may ask: can it happen in real life.
- Hypothetical estimands often suffer from non-positivity (e.g. what would happen if this person would have never be treated for his bloodpressure of + 200 mmhg?).
- A guideline may be that a researcher who proposes a new estimand should be able to give one example where the estimand would be useful, and an example where the estimand is not estimable because assumptions do not hold ('where does the method break down’?).
- There is the issue of explaining the estimand to other statisticians, and to explain the estimand to clinicians.
- We also discussed that a 4 phase process of development of causal estimands, analogous to the development of new statistical theory discussed in a talk by Georg Heinze, may be sensible. In that approach, phase one would be the definition of new estimands, with a careful listing of identifiability assumptions. The next phases would consider interpretability of the estimand and sensibility of assumptions.
- Assumptions should be biologically plausible.
- Estimands should focus on a “real” population.

Next steps:

- Jonathan Bartlett found an interesting paper on dementia (quality of life with mixed models), so we should ask him to send it to us.

- Send this report around and ask who else would be interested
- set up a meeting to discuss plans.