Navigating treatment discontinuation in emulated trials: A closer look at the intention-to-treat principle

Anders Munch, Kathrine Kold Sørensen, Christian Torp-Pedersen & Thomas Alexander Gerds

Section of Biostatistics
University of Copenhagen

The task

Emulate target trials in register data (electronic health records) and use longitudinal causal inference to hopefully (!) resemble results of previous randomized clinical trials.

It has been suggested several times* to compare the intention-to-treat analysis of the RCT with an intention-to-treat analysis of the corresponding emulated target trial.

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*WP4 of REDDIE
Emulation of cardiovascular outcome trials in diabetes (LEADER, EMPA-REG)

Notation

RCT-ITT = Intention-To-Treat analysis of a Randomized Clinical Trial

RWD-ITT = Intention-To-Treat analysis of an Emulated Target Trial in Real World Data

Summary and conclusions

- RCT-patients deviate from protocol less likely and for other reasons than RWD-patients.
- The ITT estimands are not a priori well defined – they depend on how patients deviate from protocol during the followup period.
- A well defined estimand is needed in order to make oranges from apples.

The  estimand seems to resemble the real-life effect of the treatment better than the  estimand.

But: it deserves a different name (suggestions?)

Oranges

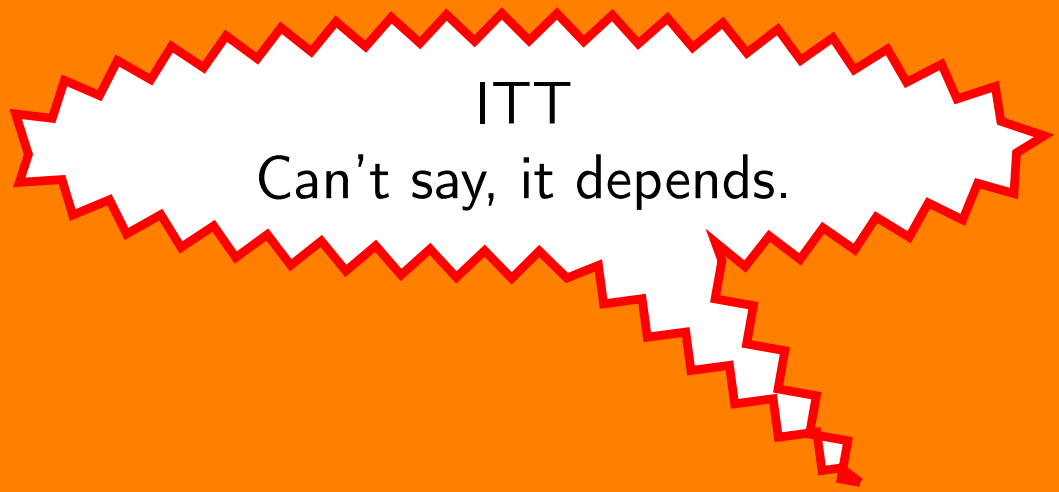
The intention-to-treat principle

In randomized trials, the intention-to-treat principle estimates the effect of the treatment policy (the effect of randomization). Applying the intention-to-treat principle doesn't solve the problem:

> When treatment is effective and non-adherence occurs, the intention-to-treat analysis underestimates the magnitude of the treatment effect that will occur in adherent patients.

The statistical analysis is simple, but what is the estimand?

Hej, what are you estimating?



Guidelines for RCTs: ICH 9

It remains undisputed that randomisation is a cornerstone of controlled clinical trials and that analysis should aim at exploiting the advantages of randomisation to the greatest extent possible.

However, the question remains whether estimating an effect in accordance with the ITT principle always represents the treatment effect of greatest relevance to regulatory and clinical decision making.[1]

[1] ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials

Compliance and adherence in RCTs

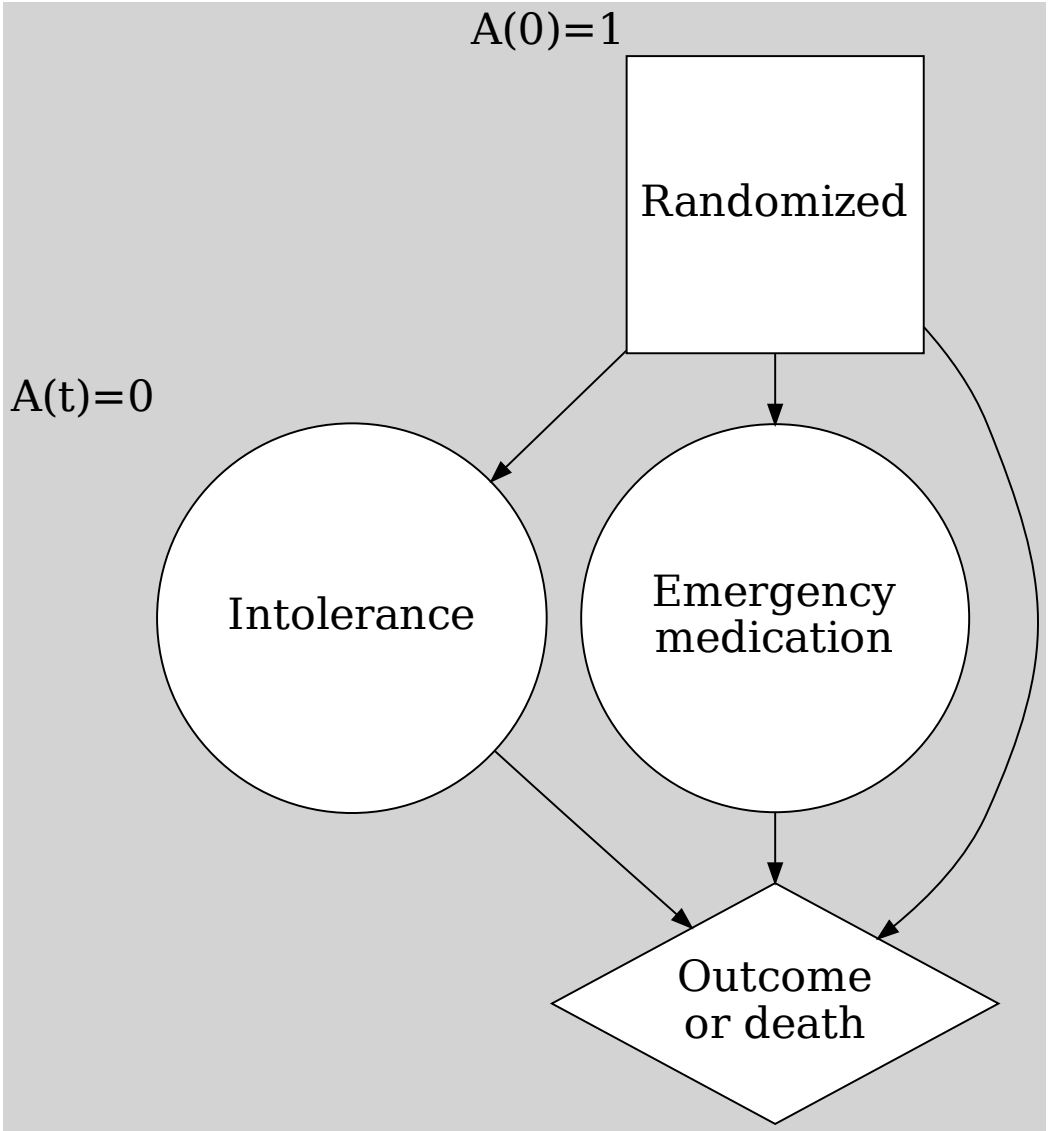
Patients are selected to minimize intolerance and maintained to maximize compliance/adherence.

Intercurrent events such as treatment discontinuation, treatment holidays, modification or use of emergency medication do occur.

These can and should be incorporated in the protocol ("censored" versus competing risk).

The intention-to-treat estimand depends on the non-compliance and non-adherence behaviour of the trial population during followup (post-randomization) and is first defined once the trial is completed.

Randomized Clinical Trial deviations from protocol



Example: LEADER trial

Patients were randomized to liraglutide vs placebo.

Patients started insulin during followup (drop-in).

Patients had treatment holidays.

The intercurrent events are recorded and reported. They affect the interpretation of the 

Apples

Emulated target trials – example from Hernan & Robins[2]:

Treatment strategies (agree)

- Refrain from taking hormone therapy during the follow-up.
- Initiate hormone therapy and remain on it during the follow-up.

Analysis plan (disagree)

- Intention-to-treat effect: estimated via comparison of 5-year cancer risks among individuals assigned to each treatment strategy.
- Per-protocol effect: estimation requires adjustments for pre- and postbaseline prognostic factors associated with adherence to the strategies of interest.

[2] *Using big data to emulate a target trial when a randomized trial is not available* Am J Epidemiol. 2016;183(8):758–764

Example from Hernan & Robins: modified strategies

Treatment regimens (emulated trial 1, per protocol)

- Refrain from taking hormone therapy during the follow-up.
- Initiate hormone therapy and remain on it during the follow-up.

Treatment regimens (emulated trial 2, "intention-to-treat")

- Refrain from taking hormone therapy at time zero, then allow initiation during the follow-up with the same likelihood as observed in the data.*
- Initiate hormone therapy, then allow treatment stop with the same likelihood as observed in the data.*

* The strategy is only well-defined when the hypothetical protocol specifies a (probabilistic) process dictating post treatment-baseline.

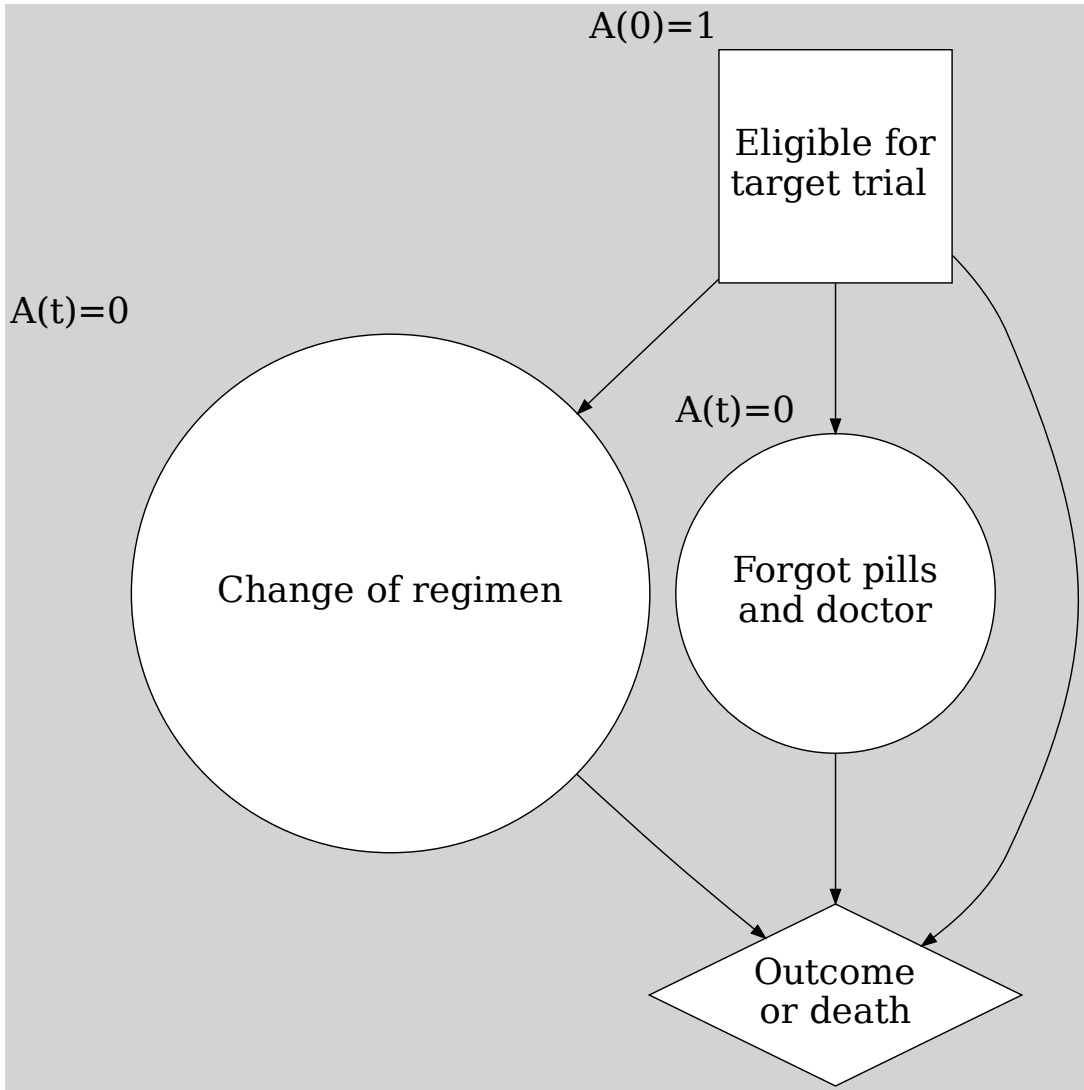
Emulated target trials in observational data

In the register data:

- Patients were not actually randomized.
- There is no protocol (that we can access).
- Treatment strategies are likely diverse and can change dynamically in the study (calendar) period and also in the individual followup period.
- Reasons for deviations from a hypothetical treatment regimen are typically not registered.

The term “intention-to-treat” seems inappropriate.

Real world data deviations from initial treatment



Example: emulating the LEADER trial in Danish registers

Patients initiate GLP1-RA, SGLT2i, DPP4i, SU, TZD ...

Patients switch, add, stop, forget, pause treatment and also take drop-in medicine (insulin).

We cannot distinguish intolerance from forgotten pills in the register data.

We can ask *what if* a patient who really initiated DPP4i would have initiated GLP1-RA instead and vice versa.

What is the estimand?

High hanging fruit

Treatment deviation propensity process

Ideal trial

$$P(A(t) = 0 | T \geq t, \bar{X}(t)) = 0$$

Randomized clinical trial

$$P(A(t) = 0 | T \geq t, \bar{X}(t)) = P(\text{intolerance} | T \geq t, \bar{X}(t)) + \cdots$$

Danish register data

$$P(A(t) = 0 | T \geq t, \bar{X}(t)) = P(\text{intolerance} | T \geq t, \bar{X}(t)) + P(\text{forgot the pills} | T \geq t, \bar{X}(t)) + \cdots$$

Possible treatment strategies for emulated trials

1. The ideal trial
   - Take GLP1-RA for 5 years
   - Take SGLT2i for 5 years
2. The trial which targets the ITT estimand of the RCTs
   - Take GLP1-RA for 5 years but deviate with the same probability as observed in LEADER*
   - Take SGLT2i for 5 years but deviate with the same probability as observed in EMPA-REG*
3. The trial which targets the effect of treatment initiation under real world conditions
   - Take GLP1-RA for 5 years but deviate with the same probability as observed in registers*
   - Take SGLT2i for 5 years but deviate with the same probability as observed in registers*

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* For these to be well-defined one has to pre-specify a propensity process

Discussion

The intention-to-treat estimands are not well defined:
they depend on how the patients in the RCT/RWD study deviate from the protocol/hyptothetical regime.

The RWD emulated trial analysis which "randomizes" patients only at time zero may make sense but it does not target the same estimand as the ITT analysis of the RCT.