Analysing observational datasets with treatment switches or non-adherence – emulating a Target Trial

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Dr Nicholas Latimer (n.latimer@sheffield.ac.uk)
Reader in Health Economics, School of Health and Related Research, University of Sheffield, UK

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Analysing observational datasets

- Ideally we use RCTs to estimate comparative effectiveness
- If we can't run an RCT, we can try to emulate one using observational data
- **"Target Trial"**: Framework for analysing observational data recently introduced in the epidemiological literature
  (Hernan MA, Robins JM. American Journal of Epidemiology;183(8) 2016)
- **Who is familiar with this approach? Has anyone ever conducted a Target Trial analysis?**

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The Target Trial approach (Hernan & Robins, 2016)

- There are 7 key components of the target trial protocol:
  1. Eligibility criteria
  2. Treatment strategies
  3. Assignment procedures
  4. Follow-up period
  5. Outcome
  6. Causal contrasts of interest
  7. Analysis plan

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The Target Trial approach (Hernan & Robins, 2016)

- There are 7 key components of the target trial protocol:

1. Eligibility criteria

→ Only include people that would satisfy the eligibility criteria of our Target Trial
→ Likely to need data on things like line of therapy, performance status

2. Treatment strategies

→ Likely to only be able to emulate a pragmatic trial
→ Assign eligible people to the 'trial' treatment strategy that is consistent with their baseline data
→ "New user" design, to avoid bias associated with selection of individuals who meet eligibility criteria after initiation of a treatment

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The Target Trial approach (Hernan & Robins, 2016)

- There are 7 key components of the target trial protocol:

3. Assignment procedures

→ Cannot emulate blinding
→ To emulate random assignment at baseline, must adjust for confounding factors to assure comparability of treatment groups
→ Standard regression adjustment sufficient to adjust for baseline confounders
→ Can only successfully emulate trial if no unmeasured confounding at baseline

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The Target Trial approach (Hernan & Robins, 2016)

- There are 7 key components of the target trial protocol:

4. Follow-up period

→ Need to define time zero (baseline) at which eligibility criteria are met and after which outcomes begin to be counted
→ Usually when an eligible individual starts a treatment strategy

5. Outcome

→ Use the dataset to identify if and when the outcome occurs
→ Can't emulate systematic and blind outcome ascertainment. Death is one of the least problematic outcomes to analyse

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The Target Trial approach (Hernan & Robins, 2016)

- There are 7 key components of the target trial protocol:

6. Causal contrast of interest

→ ITT analysis is awkward in an observational data – "initiating" ≠ "assignment"
→ Usually estimate per-protocol (PP) effect (effect if treatment strategy defined was adhered to)
→ Note, the causal contrast of interest will depend upon the estimand of interest

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The Target Trial approach (Hernan & Robins, 2016)

- There are 7 key components of the target trial protocol:

7. Analysis plan

→ Time-dependent confounding is important in observational analyses when:
→Treatment switching occurs
→Adherence changes over time
→People are censored when they stop adhering to a defined treatment strategy (i.e. PP analysis)

Example: metastatic disease variable (*m*)
Treatment decreases pr(*m*)
m increases pr(*switch*)
m is prognostic for survival

→ Can't include *m* as time-dependent variable in standard regression because part of treatment effect is through *m*
→ Can't not adjust for *m*, due to confounding by indication
→ Need advanced techniques, like inverse probability weighting or g-estimation

Practical applications

- Harvard team working with SEER-Medicare data to demonstrate best practices for comparative effectiveness with observational data
  (Petito LC, Garcia-de-Albeniz X, Hernan MA. Assessing comparative effectiveness of cancer treatments in the SEER-Medicate linked database, StatFest 2018)

- First task: demonstrate whether approach "works" (given data available)

→ Conduct analyses in an area where an RCT exists and compare results

- First case study: adjuvant chemotherapy for Stage II Colorectal Cancer.

→ Target Trial analysis replicated findings from RCT, though precision unstable

→ SEER-Medicare contains lots of information on confounders, but authors concluded some unmeasured confounding was likely to remain

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Practical applications

- My plan:

→ Assess feasibility of Target Trial approach using the UK Systemic Anti-cancer Therapy (SACT) dataset

→ Particularly valuable if possible, given use of this dataset to resolve uncertainty over effectiveness/cost-effectiveness of drugs placed in the Cancer Drugs Fund (see poster PCN317 on Wednesday morning)

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Discussion

- Target Trial approach→ neat way of formulating observational analyses
- Used correctly, can allow appropriate adjustments to be made for treatment switches or non-adherence in observational data

- **Data collection is critical**. Can only be successful if good quality data are available on baseline and time-dependent confounding factors

→ Suggestions of suitable datasets?

- Target Trial facilitates better observational data analyses

→ **Does not mean RCTs not needed**. But if we're collecting observational data, we should use it to its full potential

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