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

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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?
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
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

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
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

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 $pr(\text{switch})$
- $m$ 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-Medicare 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

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)
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