Accounting for treatment switching/discontinuation in comparative effectiveness studies

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Treatment switching can cause bias in estimates of treatment effects in observational studies

- Standard ITT/initiated treatment analysis doesn’t answer the question we’re interested in
- To answer the decision problem, we need to estimate (model) what would have happened if there had been no switching

PFS, Progression-free survival; PPS, Post-progression survival; OS, Overall survival

Inadequate methods used to account for treatment switching

- Unadjusted regression models (ITT approach): assume that treatment switching occurs randomly; only adjust for baseline confounders
- Models that exclude and censor switchers: assume that there are no confounders that affect both the reason for switching and the treatment outcome
- Models with time-varying covariates with simple regression: assume that switching is not affected by prior treatment levels while affecting the outcome

Proposed methods to account for treatment switching

- Marginal structural models with inverse probability of censoring weights
  - Switchers are censored from the analysis; non-switchers are given larger weights than switchers with similar histories

- Structural nested failure time models with g-estimation, -formula, or -computation
  - Produce an unbiased estimate of treatment effects on outcomes in studies with treatment switching
  - Construct a pseudo-population to hypothesize the outcome of switchers if they had not switched to an alternative treatment


The Target Trial approach

- Framework for analyzing observational data to facilitate appropriate adjustments to be made for treatment switching/discontinuation
- The approach comprises seven key components relating to data collection and analysis

This will be covered in more detail later in the workshop…

Literature review of methods used

- Eligible studies:
  - Non-interventional studies comparing the effectiveness of at least two products
  - Title/abstract included mention of treatment switching/discontinuation
  - Published from 1 January 2016
- Eligible studies were identified using PubMed/MEDLINE

PRISMA diagram presenting the selection of eligible studies
Most articles were excluded during abstract review owing to switching/discontinuation not being mentioned in the title/abstract

Most studies identified did not account for treatment switching/discontinuation

- Of the 17 studies, only one included sensitivity analyses to account for switching/discontinuation:
  - Most studies employed an ITT approach, assuming that switching/discontinuation occurs randomly and therefore can be ignored
  - One study compared the outcomes of ‘early switchers’ to a treatment with patients who received that treatment alone

Method used to account for treatment switching/discontinuation, n = 17
ITT, n = 14
Sensitivity analyses to account for issue, n = 1
Substudy of ‘early switchers’, n = 1
Completer vs disconter, n = 1


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Case study: Choy et al. 2017

- Study comparing the clinical effectiveness of tocilizumab and tumor necrosis factor inhibitors in patients with rheumatoid arthritis who have not responded to conventional synthetic DMARDs

- Sensitivity analyses used to confirm results of primary effectiveness analysis
  - Multiple imputation model used to account for treatment switching/discontinuation
  - Propensity scores calculated using multiple logistic regression with covariates including:
    - Stopped previous treatment (owing to lack of efficacy)
    - Stopped previous treatment (owing to intolerance)

DMARD, disease-modifying antirheumatic drug

Widespread adoption of effective methods is warranted

Unadjusted regression models
Excluding/censoring switchers
Time-varying covariates w/simple reg
Marginal structural models
Structural nested failure time models w/g-estimation
Target Trial approach
Thank you