Global Medical Affairs
RWE and Digital

Accounting for treatment switching/discontinuation in comparative effectiveness studies

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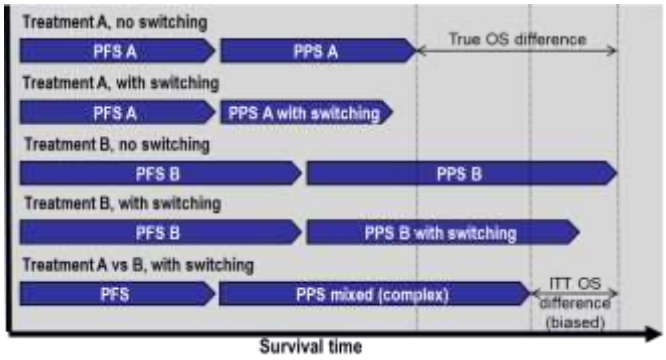
Treatment switching can cause bias in estimates of treatment effects in observational studies



- 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

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Inadequate methods used to account for treatment switching[1]

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

1. Pazzagli *et al*. Pharmacoepidemiol Drug Saf. 2018;27:148–60

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Proposed methods to account for treatment switching[1]

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

1. Pazzagli *et al*. Pharmacoepidemiol Drug Saf. 2018;27:148–60

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The Target Trial approach[1]

- 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…

1. Hernan *et al*. Am J Epidemiol. 2016;183:758–64

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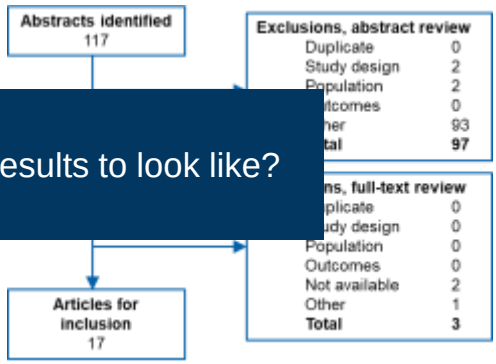
Literature review of methods used

- Eligible studies:
  - Non-interventional studies comparing the effecti[illegible] two produ[illegible]
  - Title/abstr[illegible] treatment[illegible]
  - Published [illegible]
- Eligible studies were identified using PubMed/MEDLINE

What do you expect the results to look like?



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

PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses

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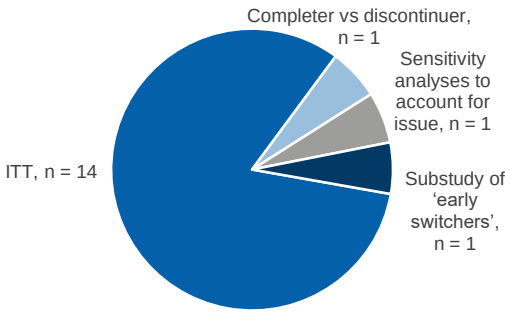
Most studies identified did not account for treatment switching/discontinuation

- Of the 17 studies, only one included sensitivity analyses to account for switching/discontinuation[1]
  - 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[2]



Method used to account for treatment switching/discontinuation, n = 17

ITT, intention-to-treat

1. Choy *et al*. Arthritis Care Res. 2017;69:1484–94
2. Turpie *et al*. Thromb Res. 2017;155:23–7

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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[1]
- 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

1. Choy *et al*. Arthritis Care Res. 2017;69:1484–94

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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

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Thank you

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