Decoding optimal methods in treatment switching: Recommendations from oncology-inspired simulation studies

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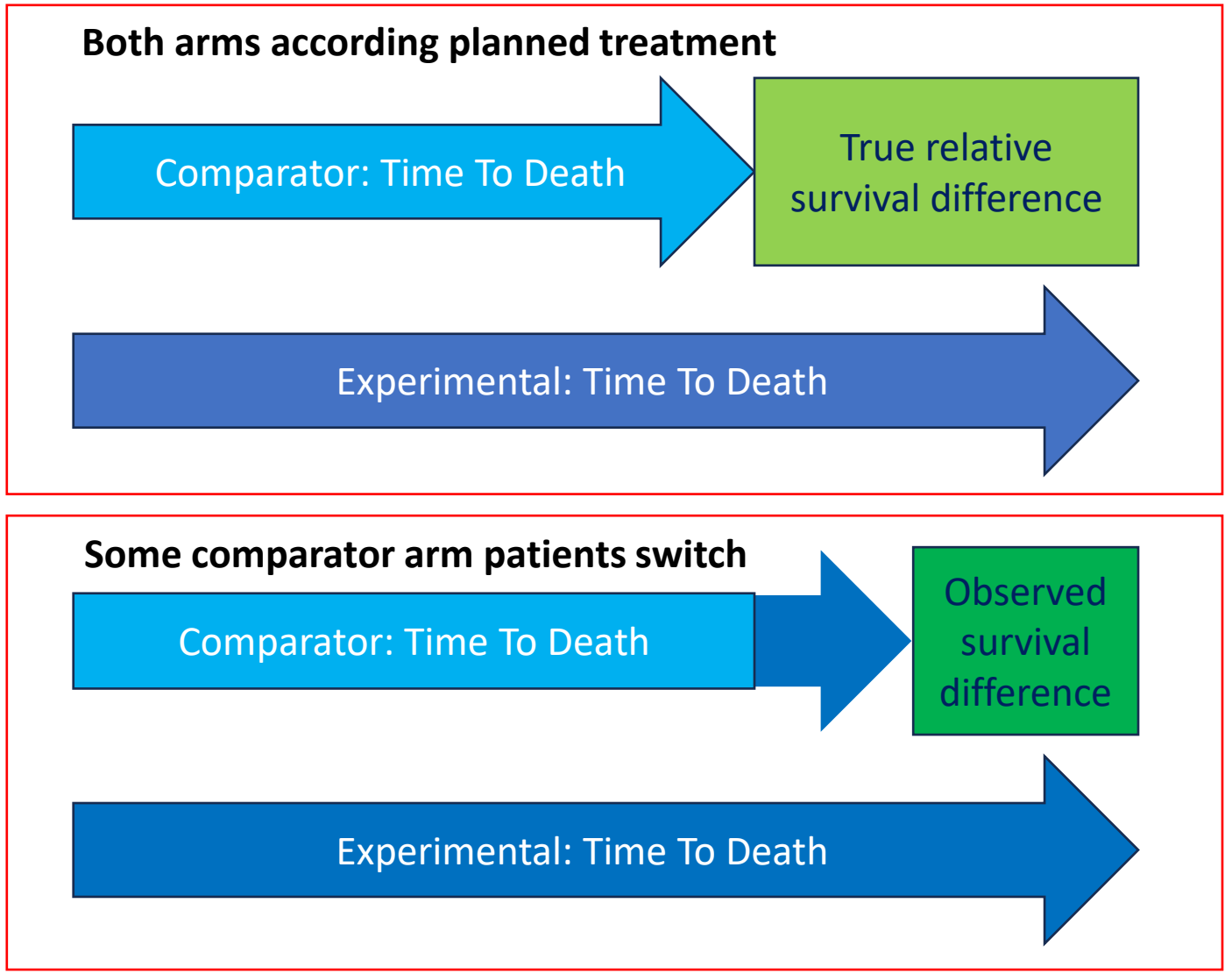
Agenda

- What is treatment switching?
- Why does treatment switching matter?
- The toolbox for treatment switching
  - IPCW
  - RPSFTM
  - TSE
- Factors influencing treatment switching
- Simulation study setups and limitations
- Factors influencing choice of adjustment method
- Conclusions

What is treatment switching?

- Patients receive subsequent therapy during RCT
  - If comparator arm patients switch, then OS is overestimated
  - Comparator OS benefits from partial contribution of more efficacious treatment
  - Survival difference is underestimated
- When to adjust
  - Sufficient numbers switch
  - Sufficient FU time after switch
  - Sufficient TE of subsequent therapy



Why does treatment switching matter?

- Regulatory (EU): Conduct sensitivity analyses for impact of cross-over for TTE endpoints *("Question and answer on adjustment for cross-over in estimating effects in oncology trials", EMA/845963/2018)*

- HTA (UK): *Section 4.6 in Modelling methods, NICE HTA Manual (31st Jan 2022)*

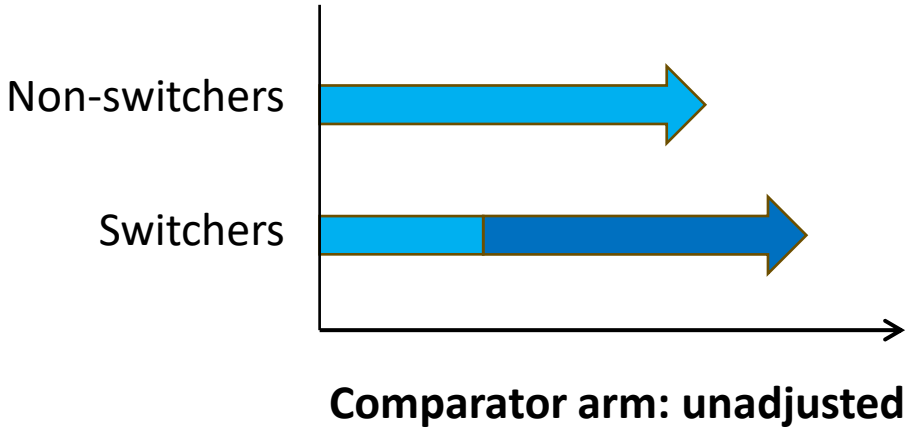
- HTA: Benefit can be either over- or underestimated: Potential changes in cost-effectiveness assessments

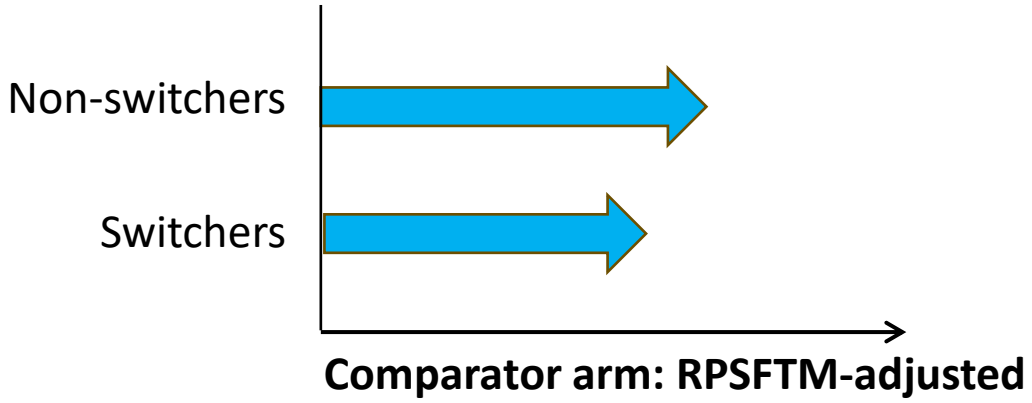
The toolbox for treatment switching: IPCW

- IPCW censors switchers at the time of switch: Informative censoring
- IPCW corrects for this bias by weighting patients
  - Fit model of treatment censoring using baseline and time-varying covariates (no unmeasured confounders)
  - Weight is inverse of probability not being censored until certain time
- If two patients have similar covariates, the one who did not switch would receive higher weights
- Carry out weighted survival analysis, such as Cox PH model or KM estimator

The toolbox for treatment switching: RPSFTM

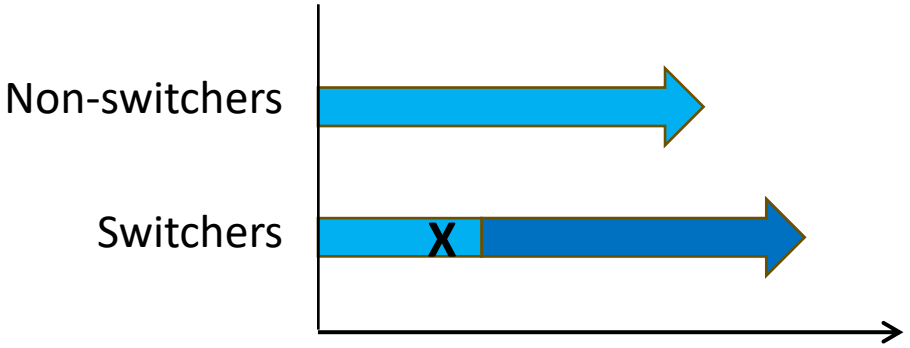
- RPSFTM adjusts treatment effect that balances counterfactual survival
- Counterfactual survival time would have been observed in absence of treatment
- Assumes constant treatment effect irrespective of start of subsequent therapy
- Adjusts survival times that would have been observed in absence of switching
- Carry out survival analysis with shrunk survival times, such as Cox PH model or KM estimator



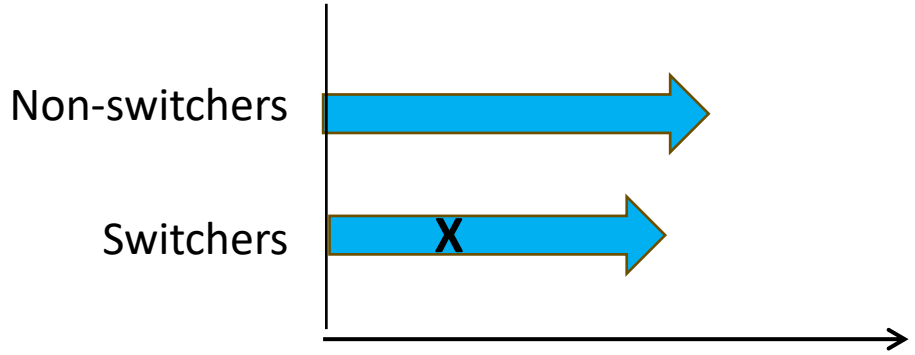


The toolbox for treatment switching: TSE

- TSE developed where switching only occurs after secondary baseline (denoted as **X**)
- Typically, this is disease progression (PD) in oncology trials
- Assumes that at secondary baseline, patients have comparable disease stage
- Switching soon after PD and no unmeasured confounders at PD
- Carry out survival analysis with shrunk survival times, such as Cox PH model or KM estimator



Comparator arm after X: unadjusted



Comparator arm after X: TSE-adjusted

Factors influencing treatment switching

- Sample Size
- Switching proportion
- Hazard Ratio
- Censor Rate
- Time-dependent confounding
- Common Treatment Effect

Simulation study setups and limitations

- Joint survival and longitudinal model: Simultaneously generate time-dependent covariate and survival times
- Switching proportions: *Low, Moderate, High*
- Treatment effect: *Low, Medium, High*
- Censoring rate: *None, Low, High*
- Time-dependent confounding: *Yes, No*
- Common Treatment Effect: *Yes, No*
- Limitations: Limited scenarios, type of switching, correct model specification

Factors influencing choice of adjustment method

- Across scenarios RPSFTM has low bias
  - IPCW with even lower bias but only for moderate switching proportions
- Without time-dependent confounding:
  - For moderate and high switching proportions TSE is best
  - For low switching proportions RPSFTM is best
- With time-dependent confounding:
  - For moderate switching proportions all three methods work well
  - For high switching proportions RPSFTM works a bit better than TSE
- No censoring not relevant in clinical trials
- Size of treatment effect (HR) of limited impact

Conclusions

- Adjusting survival times for treatment switching is crucial
- Ground truth not known in clinical trials
- Diverse scenarios are suitable to different approaches
- Trial characteristics can indicate suitable approach

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