Practical aspects of handling treatment switching in randomized clinical trials

BBS Spring Seminar

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Basel, 28 April 2016
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Outline

- Motivating example
- Time-dependent confounding
- Rank preserving structured failure time model
- Inverse probability weighting
- General recommendations
- Recent publications and existing software
- Acknowledgements
- References
Motivating example
*Everolimus in mRCC (RECORD-1)*

  - Double-blind, multicenter study with patients randomized to receive either everolimus (n = 277) or placebo (n = 139)
  - Primary endpoint PFS (HR=0.30, 95% CI 0.22-0.40, p<0.0001)
  - Regulatory approval based on PFS
- Protocol allowed crossover from placebo to everolimus upon progression
~80% of placebo randomized patients switched to everolimus

- ITT analysis of OS: HR=0.87, 95% CI: 0.65-1.15, p-value=0.162
- ITT analysis provides a valid assessment of the treatment policy
- What about assessment of treatment effect of everolimus on OS if placebo patients never received everolimus?
Time-dependent confounding

1 – Effect of interest
2 – Confounding effect on occurrence of the outcome
3 – Confounding effect on future exposure to treatment
Rank preserving structural failure time (RPSFT) model

- Estimate the **survival time gained/lost by receiving active treatment** (i.e. either randomized or “cross-over” active treatment)
- Main assumption: **treatment is acting by multiplying survival time by a given factor once patient starts receiving active treatment** (transparent but un-testable assumption)
- Multiplicative factor interpreted as relative increase/decrease in survival if one took active treatment compared to taking control
- It works by reconstructing the survival duration of patients, as if they had never received active treatment
RPSFT – acceleration factor

Treatment multiplies life by acceleration factor $\exp(-\Psi)$

$\Psi < 0 \rightarrow$ time on experimental therapy extends life compared to control

$\Psi > 0 \rightarrow$ time on control therapy extends life compared to experimental
RPSFT – G-estimation for psi (RECORD-1)

\[ \Psi = -0.66, \]

95% CI \((-2.16, 0.69)\)

**Test statistic**

**p-value**
Programming implementation for RPSFT

Data preparation
- Time to event dataset
- Covariates: stratification, baseline, exposure
- “on treatment” / “treatment group” approach
- Combined dataset

Data transformation and Statistical analysis
- G-estimation procedure
- Specify range of psi values and grid size
- For each psi value calculate U, C and test statistic
- Select psi for test statistic $\rightarrow 0$
- Dataset with original and re-censored survival time, estimated psi value
- Cox regression to estimate HR and recalculate CI
- Output:
  - Crossover corrected HR
  - KM plot
  - Psi value with CI
  - Patient level listing
The corrected results used reconstructed survival time for all control arm patients.
Inverse probability weighting (IPW) approach

- Model-based method that reweights control arm patients using propensity score methods.

- Treatment effect is expressed on the hazard ratio scale and estimated using weighted Cox model.

- Main assumption: no unmeasured confounders (all factors influencing crossover and survival are included in the model), non-testable
Inverse probability weighted analysis (IPW)

Patient in the control arm with crossover

- IPCW (weighted censoring at crossover)
- IPTW (weighted time-varying)

Patient in the control arm without crossover

- IPCW (weighted censoring at crossover)
- IPTW (weighted time-varying)

Patient in the experimental arm

- IPCW (weighted censoring at crossover)
- IPTW (weighted time-varying)

weight treatment weighted analysis

weight treatment weighted analysis

weight treatment weighted analysis
Programming implementation for IPW

Data preparation
- Time to event dataset
- Dataset with covariates (baseline, time-varying)
- Format variables for the analysis macros

Data transformation
- Split time into time intervals
- Impute missing values for time-var covariates
- Combined time to event dataset with covariates

Statistical analysis
- Subset Control arm patients
- Calculate probabilities of remaining untreated
- Datasets with probabilities per time interval
- Calculate weights for various models
- Datasets with weights
- Weighted Cox regression
- Set weight for experimental arm patients to 1
- Datasets with weights per time interval per patient
- Weighted KM plot
- Statistics for weights
- Output:
  - Crossover corrected HR, p-value
  - Weighted KM plot
  - Statistics for weights
  - Patient level listing
### Table 1. Variables Included in All Cox Regressions Models Considered

<table>
<thead>
<tr>
<th>Description</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
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<td>HR 95% CI</td>
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<td>0.29, 0.83</td>
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</table>

CI = confidence interval; HR = hazard ratio; KPS = Karnofsky performance status; MSKCC = Memorial Sloan Kettering Cancer Center.

**Model 4: best model fit (AIC)**
General recommendations

*Points to consider*

- Describe the treatment switching mechanism
  - When was switching permitted? Patient-level or study-level
  - Why did switching occur? Post-progression switch, switch based on study milestone

- Quantify the extent of switching and characterize the population of switchers
  - Number and percentage of patients who switched, proportion of total exposure and/or follow up time that was affected by switch
  - Timing of treatment switching in a form of Kaplan-Meier plot estimated median, range
  - Baseline characteristics for switchers

- Select method to account for treatment switching, implementation and description of results
  - Consider feasibility of the underlying assumptions for each method
  - Identify potential sources of bias and describe them for the method selected
  - Ideally, provide a document with the details of the model(s)
Recent publications and software

**Claire Watkins**

BBS/EFSP Europe Scientific Meeting
Application of Methods for Health Technology Assess
29th June 2015

Harvard School of Public Health – Software for MSM, SNM, etc (SAS)
http://www.hsph.harvard.edu/causal/software/

Causal inference book by Robins and Hernan – Parts of the book and the code available (in draft)

Medical Research Council – Software for RPSFT (STATA)
http://www.mrc-bsu.cam.ac.uk/software/stata-software/
Acknowledgments

- Mike Branson
- Bee Chen
- Beat Neuenschwander
- All the reviewers
References

- Korhonen P, Malangone E, Sherman S et al. Overall survival (OS) of metastatic renal cell carcinoma (mRCC) patients corrected for crossover using inverse probability of censoring weights (IPCW) and rank preserving structural failure time (RPSFT) models: Two analyses from the RECORD-1 trial. J Clin Oncol 28:15s, 2010 (suppl; abstr 4595)
Back up
An additional algorithm (‘artificial-censoring’) allows to maintain the assumption of independent random censoring required for unbiased estimation.

The artificial censoring algorithm works by shrinking the total follow-up time (time between randomization to analysis cut-off date) for all patients regardless of randomization group or treatment received.

Therefore every patient censored in the ITT analysis remains censored with duration equal or shorter to the original one; in addition, patients with an event in the original analysis may become censored via the artificial-censoring algorithm.