# Practical aspects of handling treatment switching in randomized clinical trials

BBS Spring Seminar

Viktoriya Stalbovskaya, Novartis

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# NVS Oncology Treatment Switching Guideline Team

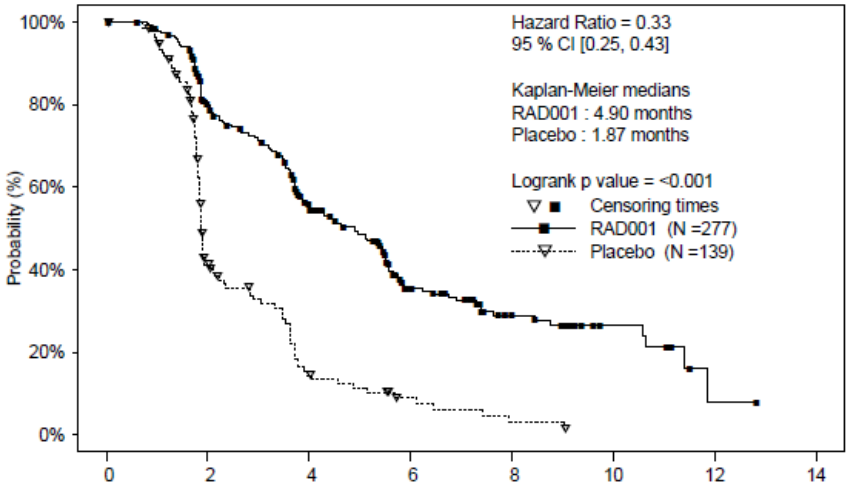
- Valentine Jehl
- Gaelle Saint-Hilary
- Santosh Sutradhar
- Zhongwen Tang
- Simon Wandel
- Nigel Yateman
- Viktoriya Stalbovskaya

# 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)*




No. of patients still at risk

| Time (months) | 0 | 2 | 4 | 6 | 8 | 10 | 12 | 14 |
|---|---|---|---|---|---|---|---|---|
| RAD001 | 277 | 192 | 115 | 51 | 26 | 10 | 1 | 0 |
| Placebo | 139 | 47 | 15 | 6 | 2 | 0 | 0 | 0 |

- Phase III study of everolimus in metastatic renal cell carcinoma Motzer et al (2008, 2010)
  - 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



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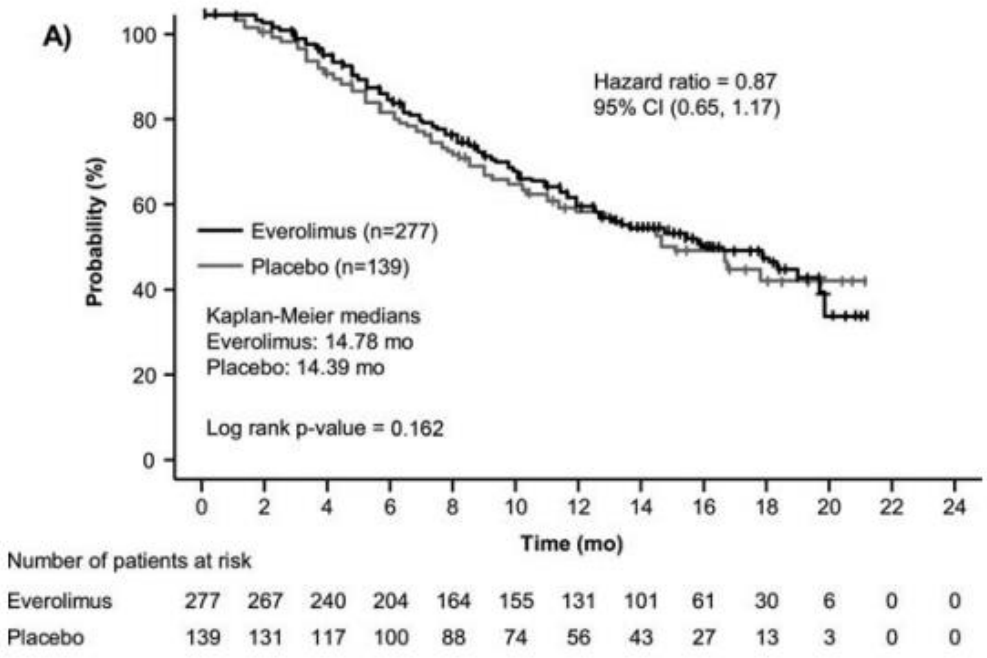
# Motivating example

*Everolimus in mRCC (RECORD-1)*




- ~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?



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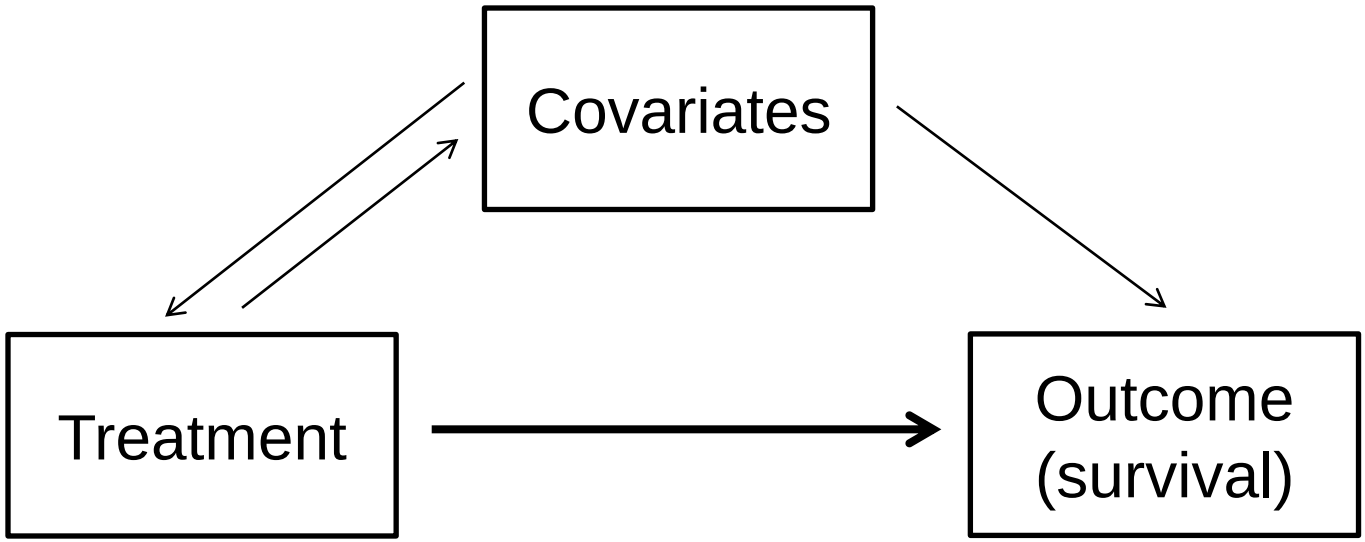
# Time-dependent confounding

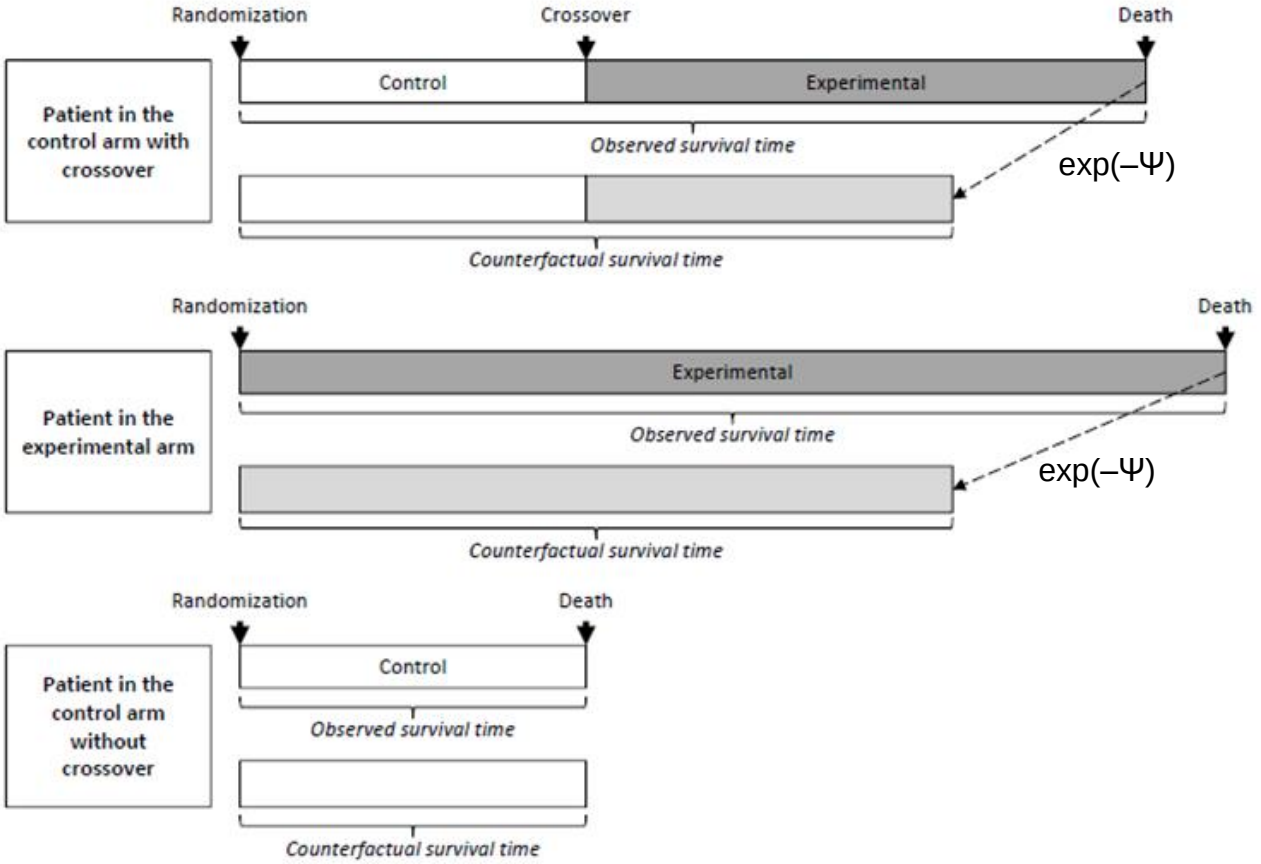



1 – Effect of interest
2 – Confounding effect on occurrence of the outcome
3 – Confounding effect on future exposure to treatment

# 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(–Ψ)

Ψ<0 → time on experimental therapy extends life compared to control

Ψ>0 → time on control therapy extends life compared to experimental



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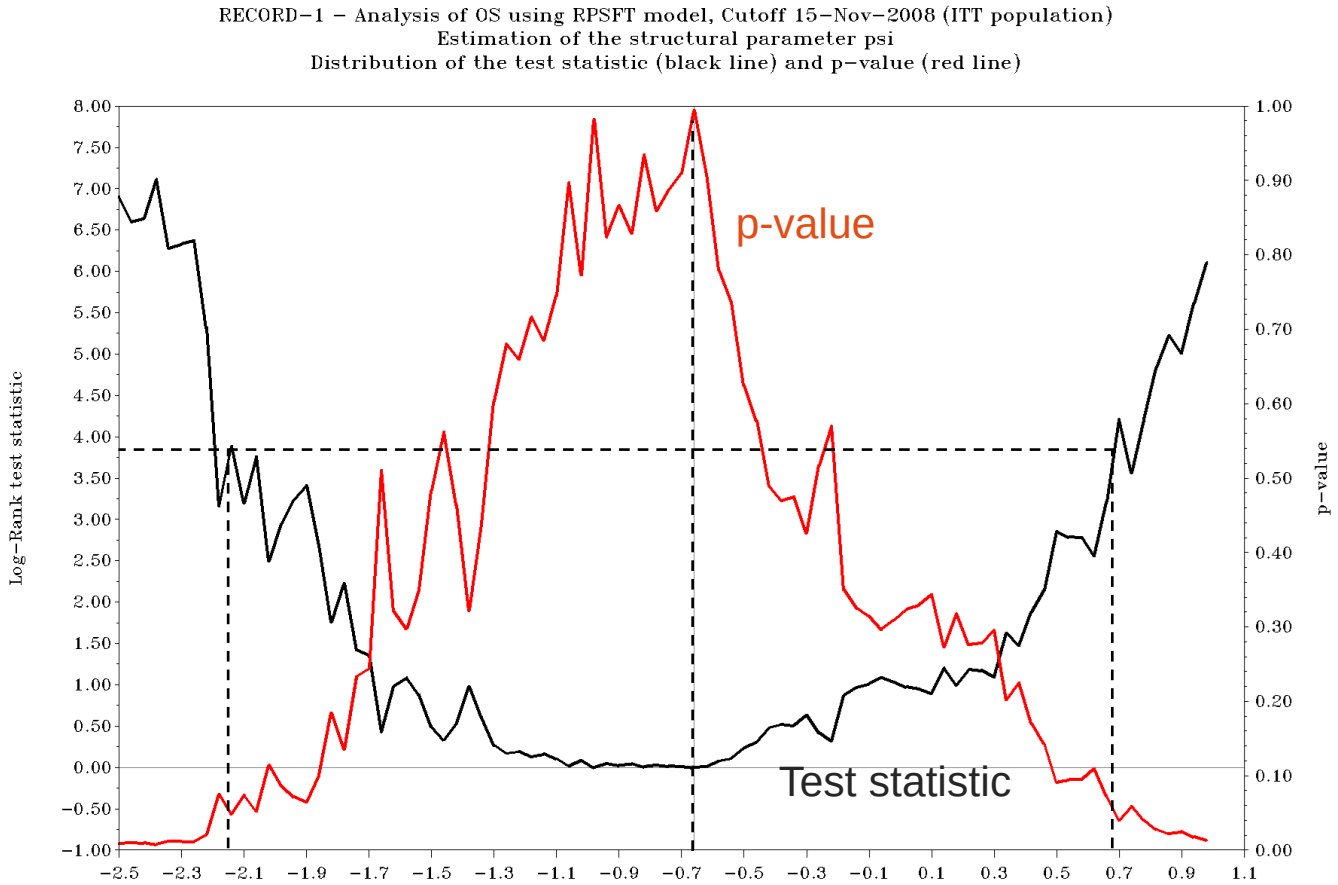
# RPSFT – G-estimation for psi (RECORD-1)




$\hat{\Psi}_{psi} = -0.66,$
95% CI $(-2.16, 0.69)$



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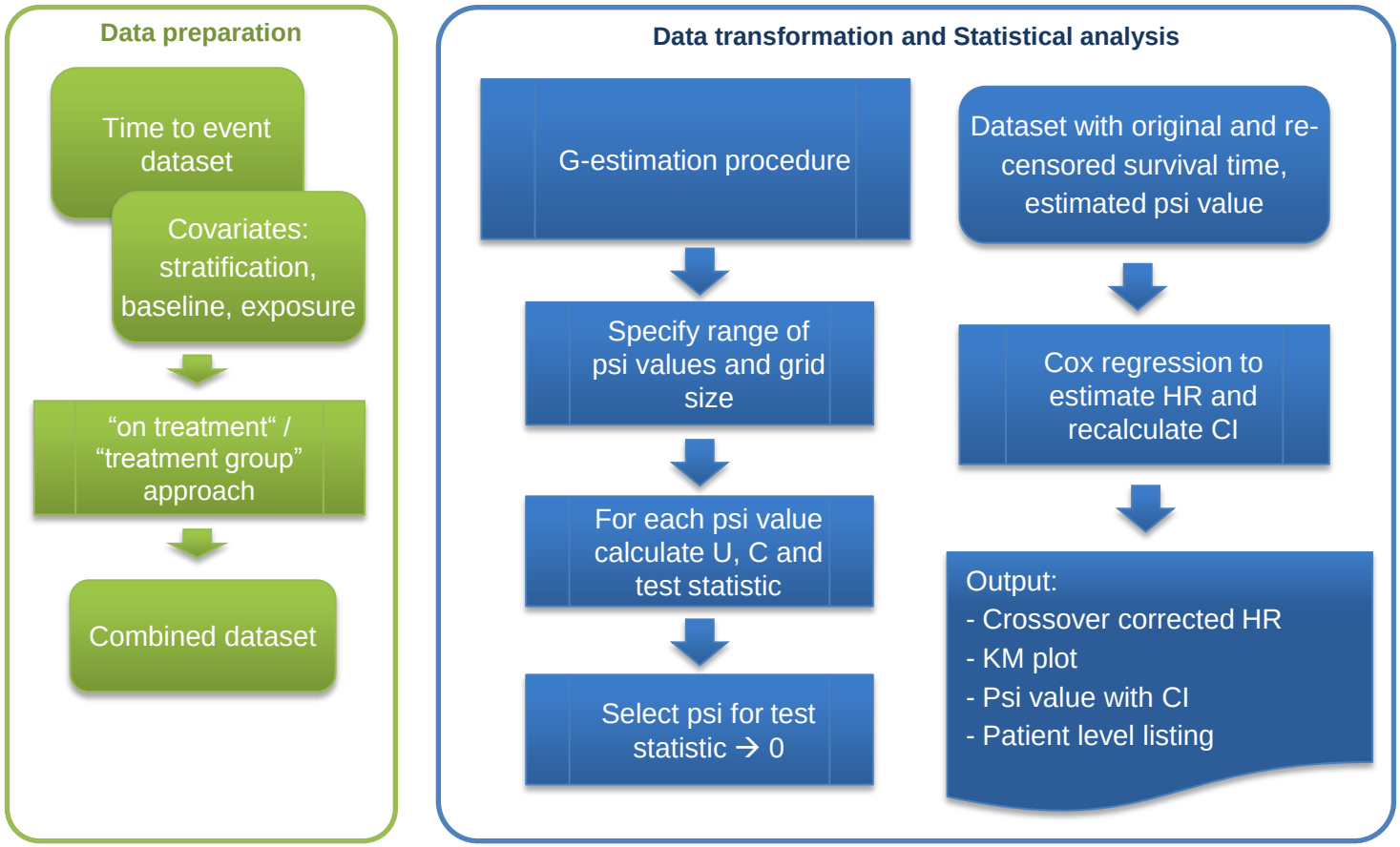
# Programming implementation for RPSFT



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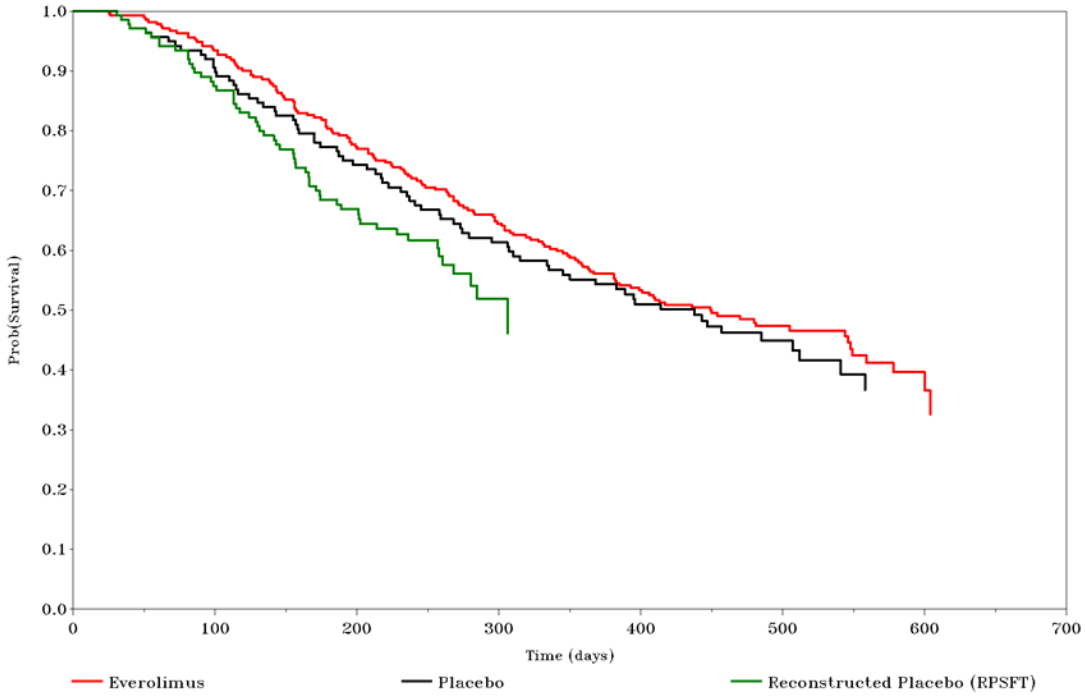
# RPSFT model results for RECORD-1




| Type of analysis | Events/Censored (Placebo) | Events/Censored (Everolimus) | Hazard Ratio | 95% CI Lower Limit | 95% CI Higher Limit |
|---|---|---|---|---|---|
| ITT analysis | 75/64 | 146/131 | 0.868 | 0.655 | 1.150 |
| RPSFT analysis | 57/82 | 146/131 | 0.603 | 0.220 | 1.651 |

The corrected results used reconstructed survival time for all control arm patients



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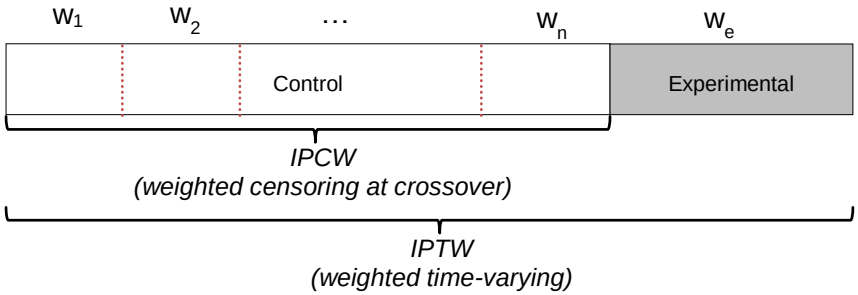
# Inverse probability weighting (IPW) approach

- 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**

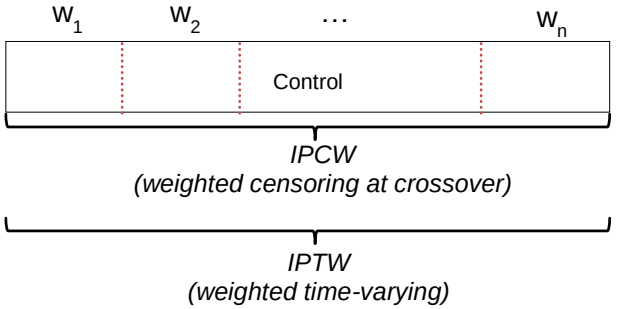



**weight**

**treatment**

**weighted analysis**

**Patient in the control arm without crossover**

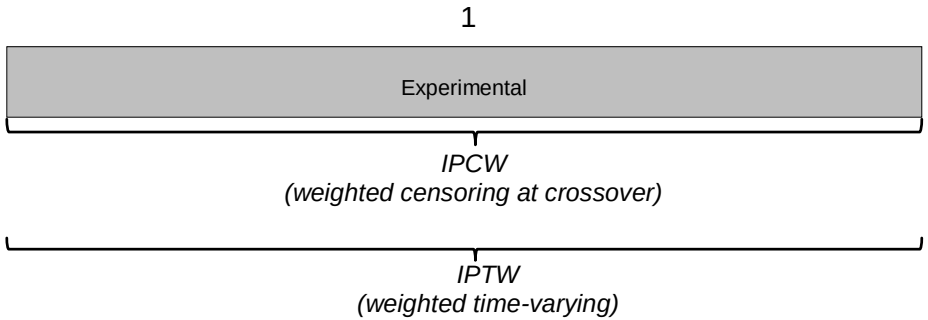



**weight**

**treatment**

**weighted analysis**

**Patient in the experimental arm**




**weight**

**treatment**

**weighted analysis**



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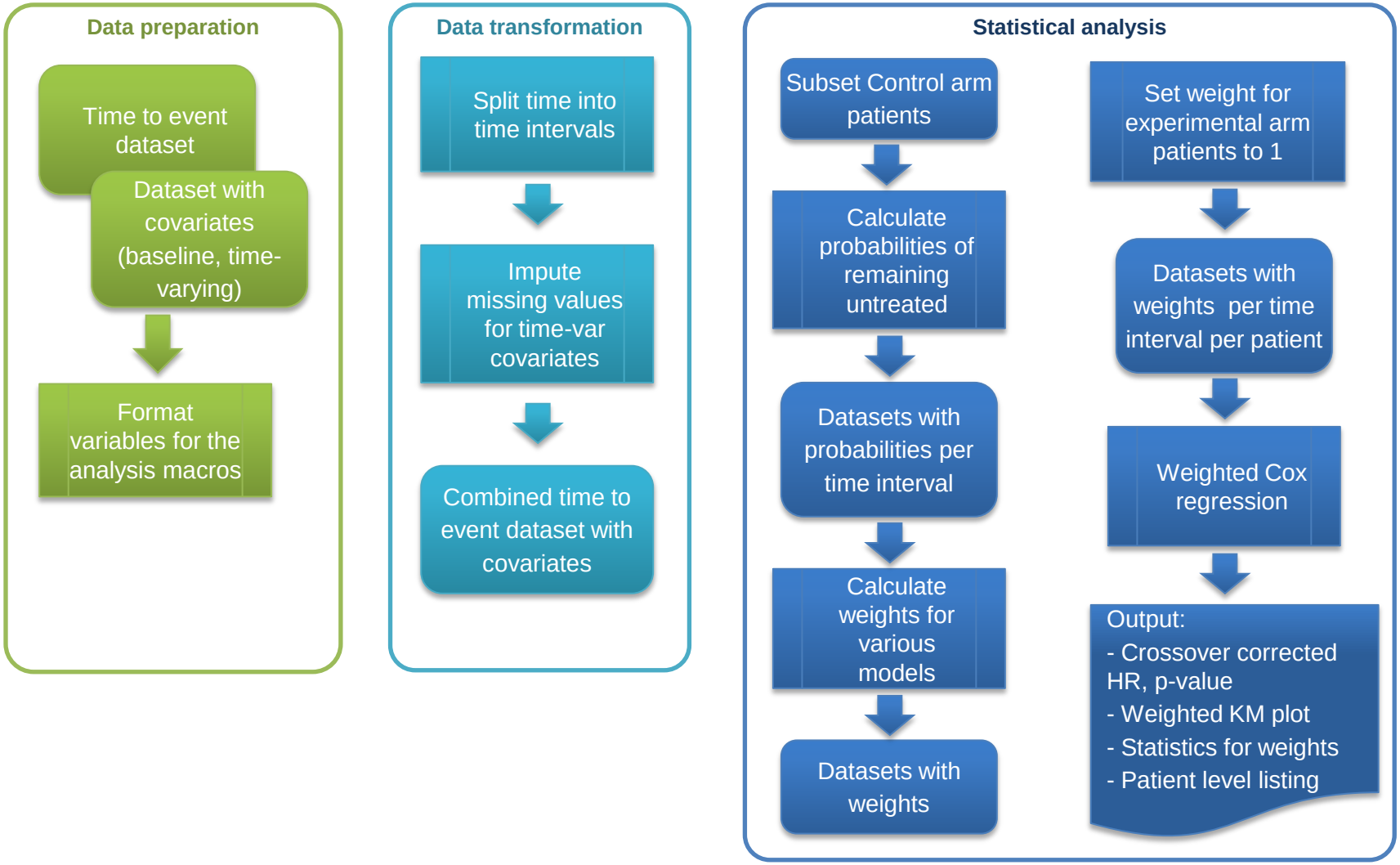
# Programming implementation for IPW



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# IPCW application to RECORD-1

**Table 1. Variables Included in All Cox Regressions Models Considered**

| Description | Model 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Age at baseline (y) | ✓ | | ✓ | ✓ | | ✓ | | | | | | | | ✓ | ✓ |
| Country | | | ✓ | | ✓ | | | | | | | | | | |
| Sex | ✓ | | ✓ | ✓ | | | ✓ | | | | | | | ✓ | ✓ |
| Race | | | ✓ | ✓ | | | | ✓ | | | | | | ✓ | ✓ |
| MSKCC prognostic score at baseline | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| KPS at baseline | | | | | | | | | | | | | | | ✓ |
| Prior treatment with sorafenib only | ✓ | | ✓ | ✓ | | | | | | | ✓ | ✓ | ✓ | | ✓ |
| Prior treatment with sunitinib only | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Prior radiation treatment | | | ✓ | ✓ | | | | | ✓ | | | | ✓ | | ✓ |
| Prior nephrectomy | | | ✓ | ✓ | | | | | | ✓ | | | ✓ | | |
| Time since diagnosis | | | ✓ | ✓ | | | | | | | | | | | ✓ |
| Liver involvement | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | |
| Bone involvement | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | |
| Randomized treatment | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Time period | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| HR | 0.54 | 0.49 | 0.45 | 0.47 | 0.50 | 0.49 | 0.53 | 0.49 | 0.50 | 0.51 | 0.44 | 0.49 | 0.51 | 0.52 | 0.49 |
| HR 95% CI | 0.30, 1.01 | 0.26, 0.92 | 0.24, 0.84 | 0.27, 0.82 | 0.27, 0.94 | 0.26, 0.91 | 0.28, 1.00 | 0.26, 0.91 | 0.27, 0.93 | 0.27, 0.96 | 0.26, 0.76 | 0.26, 0.92 | 0.27, 0.96 | 0.28, 0.98 | 0.29, 0.83 |

CI=confidence interval; HR=hazard ratio; KPS=Karnofsky performance status; MSKCC=Mem

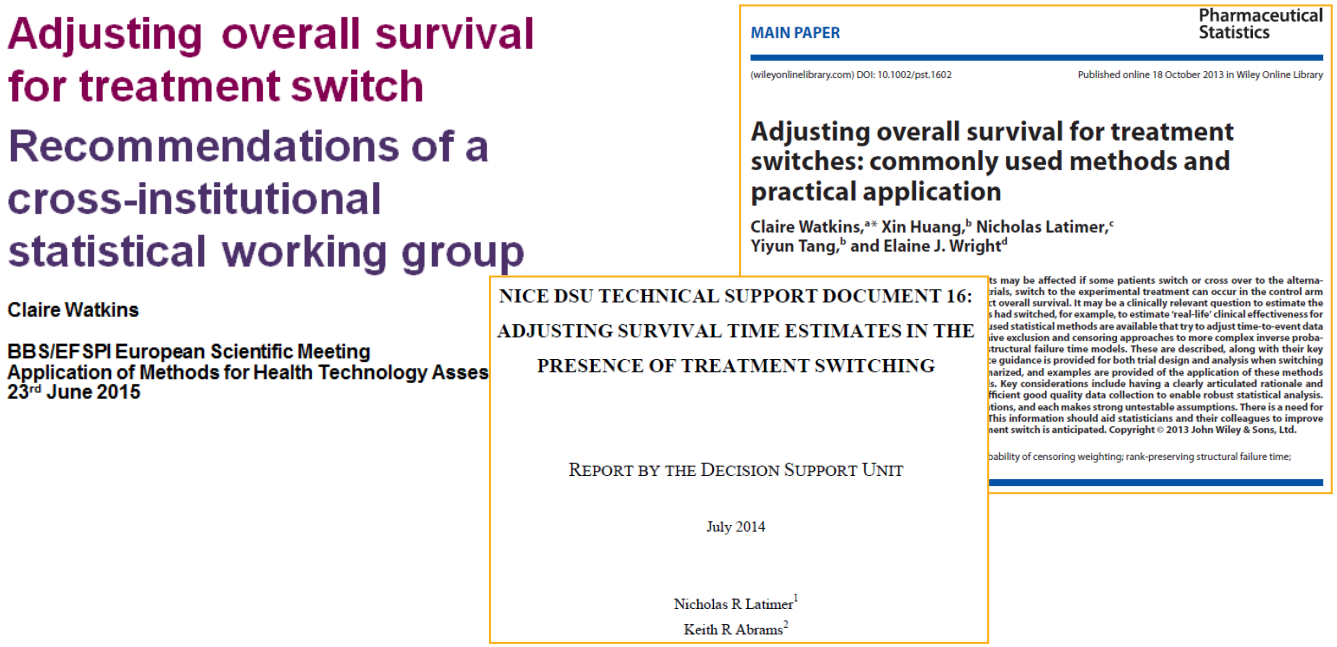
**Model 4: best model fit (AIC)**

# 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




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)
http://www.hsph.harvard.edu/miguel-hernan/causal-inference-book/

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



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# Acknowledgments


- Mike Branson
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# 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)
- Korhonen P, Zuber E, Branson M et al. *Correcting overall survival for the impact of crossover via a rank-preserving structural failure time (RPSFT) model in the RECORD-1 trial of everolimus in metastatic renal-cell carcinoma.* J Biopharm Stat 2012
- Latimer NR, Abrams KR, Lambert PC et al. *Adjusting survival time estimates to account for treatment switching in randomized controlled trials--an economic evaluation context: methods, limitations, and recommendations.* Med Decis Making 2014
- Motzer RJ, Escudier B, Oudard S et al. *Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial.* Lancet 2008
- Motzer, R., Escudier, B., Oudard, S., et al. (2010). Phase 3 trial of everolimus for metastatic renal cell carcinoma: Final results and analysis of prognostic factors. Cancer 116:4256– 4265.

# Back up



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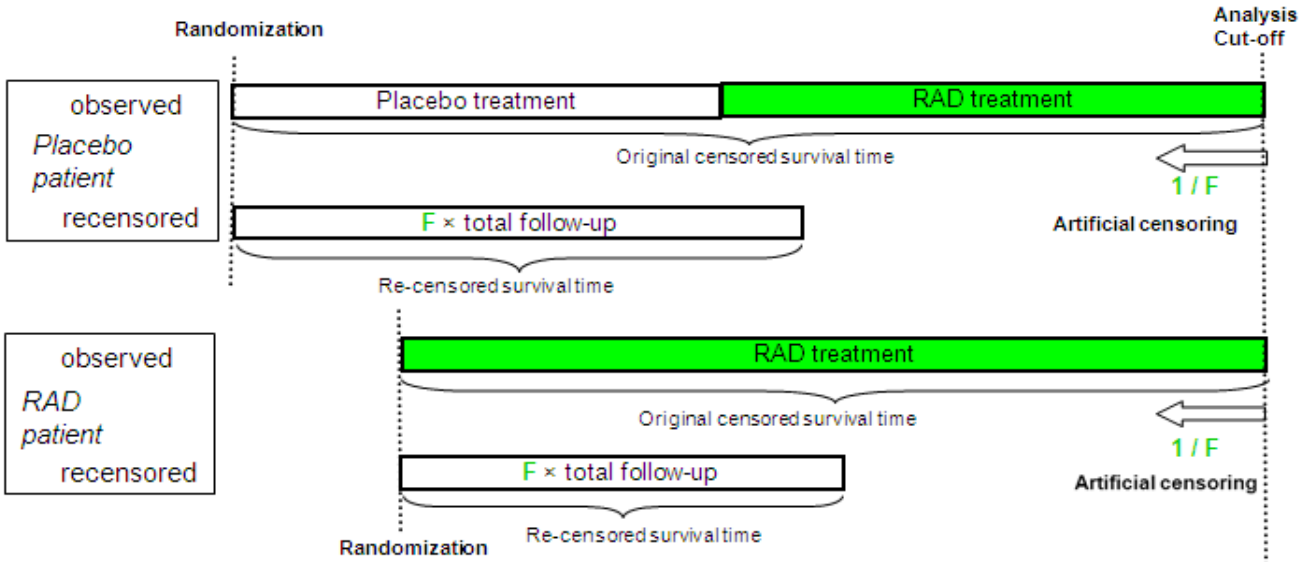
# RPSFT – Artificial censoring algorithm

- 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



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