Estimation of Treatment Effects Under Non-Compliances

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Outline

Motivation

- Setting:
  - oncological trials
  - randomized
  - two-arm studies, (placebo-)controlled

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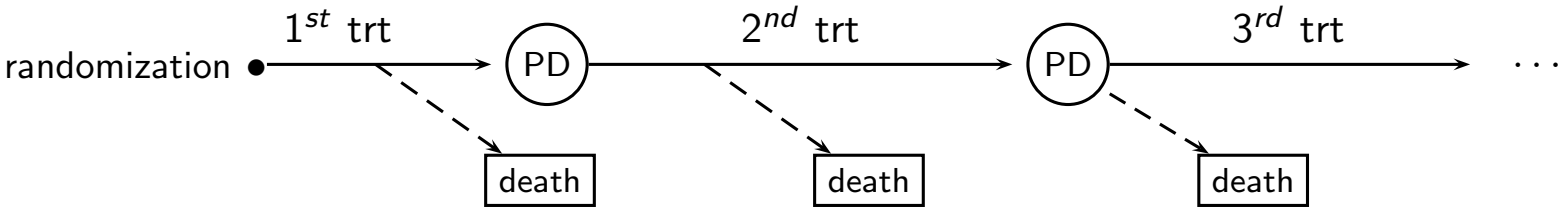

PD: progressive disease

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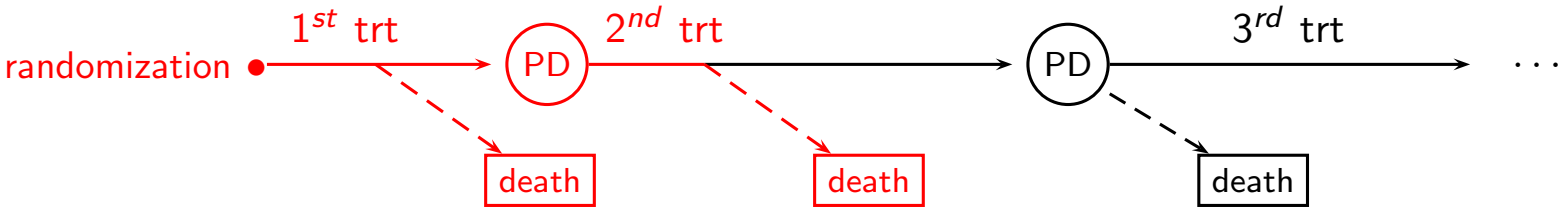


PD: progressive disease

- Setting:
  - oncological trials
  - randomized
  - two-arm studies, (placebo-)controlled
- Endpoints:
  - **Progression-free Survival** (PFS):
    $\hookrightarrow$ *time from randomization to (first) progression or death from any cause, whatever comes first*
  - **Overall Survival** (OS):
    $\hookrightarrow$ *time from randomization to death*

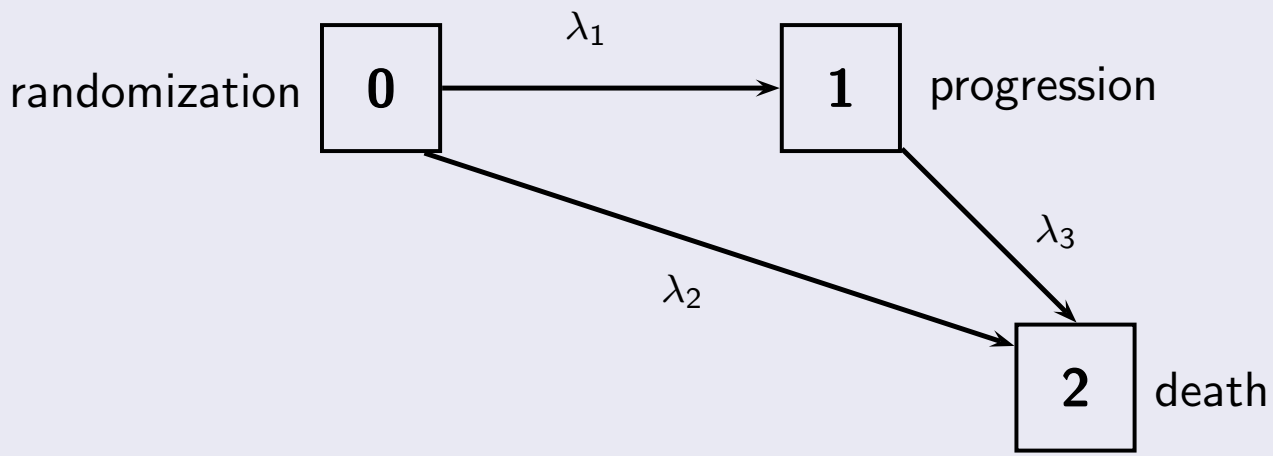
Motivation

Issue:

- controlled trial design commonly only until progression, thereafter control group might receive (similar) treatment
- non-ignorable non-compliances (e.g. because of severe side effects)

- this can lead to confounded estimates of treatment effect

Starting Point: Three-State Model



- assumption of constant transition rates between states gives exponentially distributed transition times
- PFS time is $T_{PFS} := T_0 \sim \mathrm{Exp}(\lambda_1 + \lambda_2)$
- distribution function of OS with $t \in \mathbb{R}_+$

$$F_{T_{OS}}(t) = 1 - \frac{\lambda_1}{\lambda_1+\lambda_2-\lambda_3}\, \mathrm{e}^{-\lambda_3 t} + \frac{\lambda_3-\lambda_2}{\lambda_1+\lambda_2-\lambda_3}\, \mathrm{e}^{-(\lambda_1+\lambda_2)t}$$

Rank Preserving Structural Failure Time Model

The observed lifetime T_i of subject i may be linked to his/her latent baseline survival time U_i via the RPSFTM [Robins J M, Tsiatis A A (1991)]

$$U_i = \int_0^{T_i} \mathrm{e}^{\beta_0 d_i(t)} \, \mathrm{d}t, \tag{1}$$

with β_0 the causal effect and $d_i(t)$ a treatment indicator at time t.

- RPSFTMs are models for counterfactuals, since they presume that individuals can theoretically be observed under different conditions

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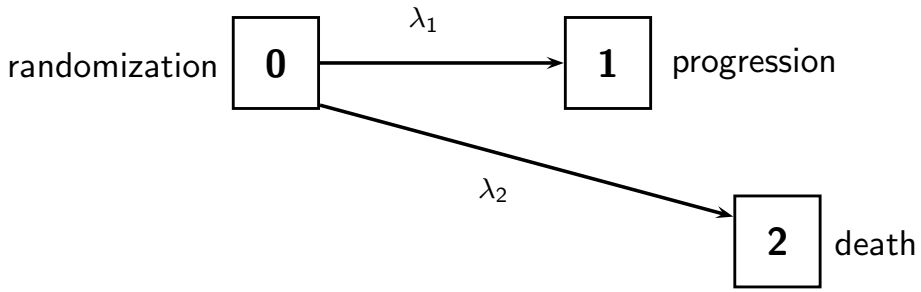
- RPSFTMs are models for counterfactuals, since they presume that individuals can theoretically be observed under different conditions
- Full compliance in treatment arm is given by $d_i(t) = 1$ for all t

$$U_i = \mathrm{e}^{\beta_0} T_i$$

- e^{β_0} fraction of increase or decrease in survival time because of treatment

Combination of Initial Models for PFS

- restriction on model for PFS



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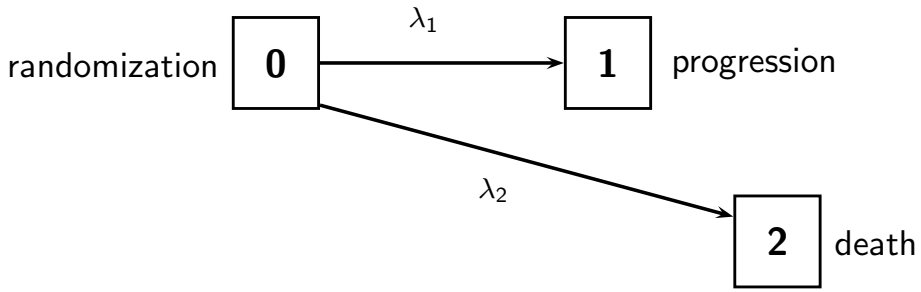
- assumption of full compliance in treatment arm



- in control arm:
  $U = T_{PFS} \sim \text{Exp}(\lambda_1^C + \lambda_2^C)$
- in treatment arm:
  $U = e^{\beta_0} \cdot T_{PFS}$ with $T_{PFS} \sim \text{Exp}(\lambda_1^T + \lambda_2^T)$

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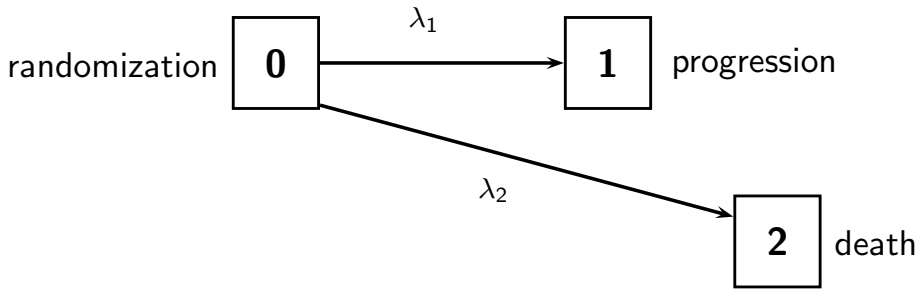

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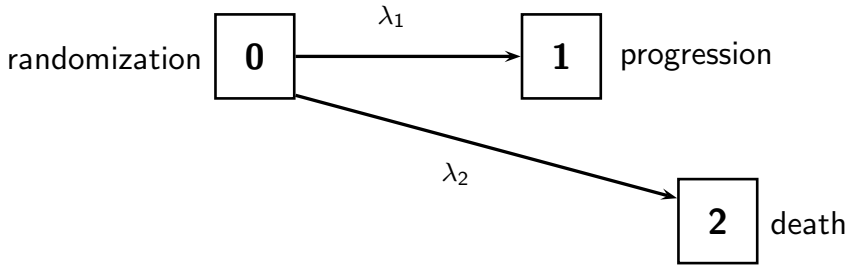
$\Rightarrow$ causal parameter of the RPSFTM is $e^{\beta_0} = \frac{\lambda_1^T + \lambda_2^T}{\lambda_1^C + \lambda_2^C}$.

Combination of Initial Models for PFS

- assumption of partial compliance in treatment arm with time on treatment given by $\tau = p \cdot T_{PFS}$, $p \in [0, 1]$



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- in treatment arm:
  $U = \int_0^\tau \mathrm{e}^{\beta_0}\,\mathrm{d}t + \int_\tau^{T_{PFS}}\,\mathrm{d}t \quad \Rightarrow \quad T_{PFS} = U \cdot \left(1 + p(\mathrm{e}^{\beta_0} - 1)\right)^{-1}$

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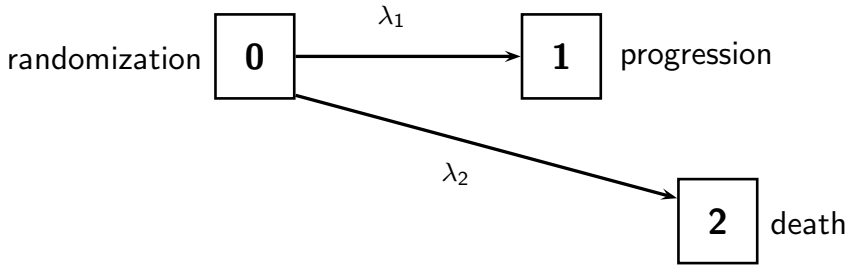

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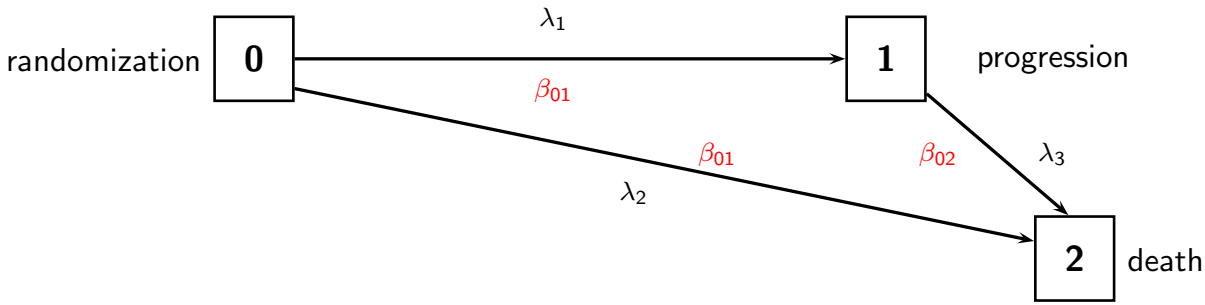
$\Rightarrow$ distribution of PFS under partial compliance is

$$T_{PFS} \sim \text{Exp}\left((1-p) \cdot (\lambda_1^C + \lambda_2^C) + p \cdot (\lambda_1^T + \lambda_2^T)\right)$$

Combination of Initial Models for PFS and OS

- assumption of full compliance in treatment arm
- 2^{nd} line treatment after progression



- RPSFTM becomes $U = e^{\beta_{01}} \cdot T_{PFS} + e^{\beta_{02}} \cdot T_1$

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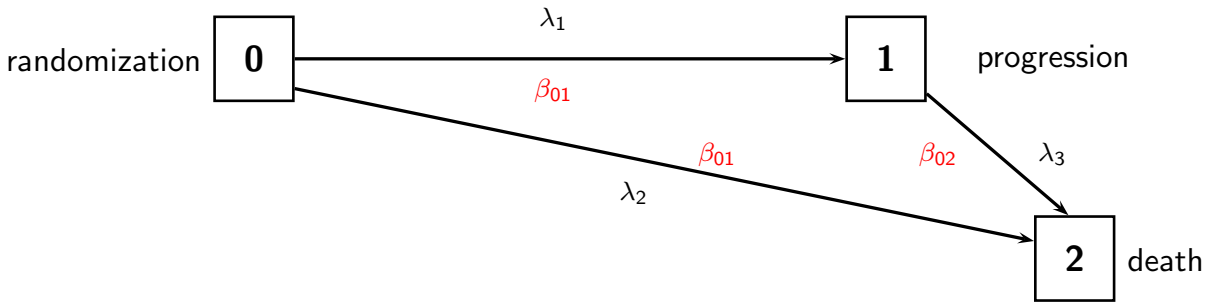

- RPSFTM becomes $U = e^{\beta_{01}} \cdot T_{PFS} + e^{\beta_{02}} \cdot T_1$
- assumption of identical progression rates in study arms

$$\frac{\lambda_1^T}{\lambda_1^T+\lambda_2^T} = \frac{\lambda_1^C}{\lambda_1^C+\lambda_2^C} \quad \text{and} \quad \frac{\lambda_2^T}{\lambda_1^T+\lambda_2^T} = \frac{\lambda_2^C}{\lambda_1^C+\lambda_2^C}$$

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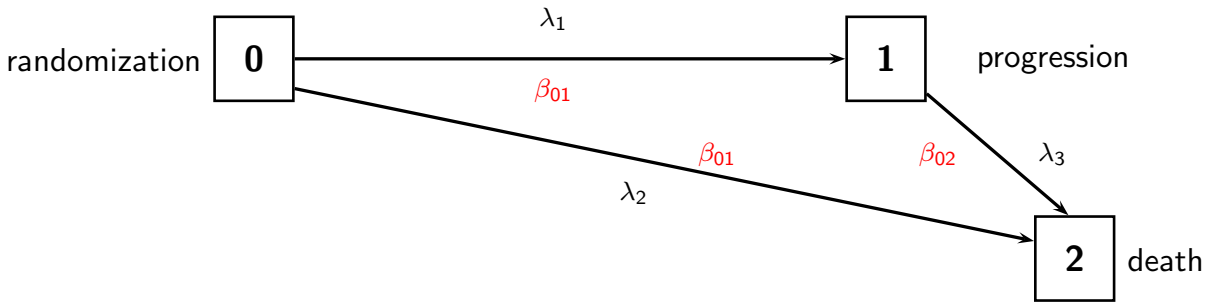

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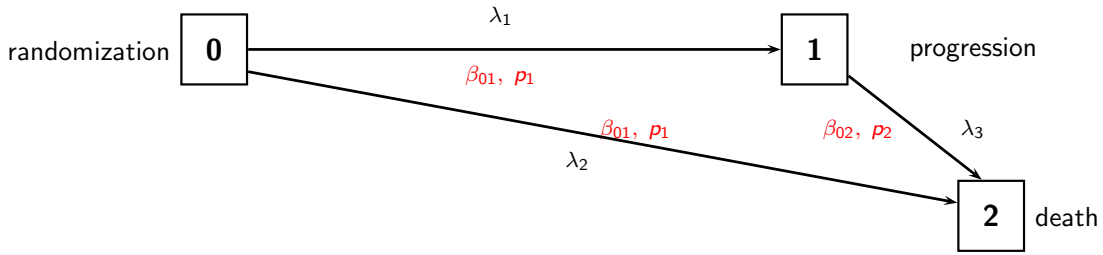
$\Rightarrow$ causal parameters of the RPSFTM are

$$e^{\beta_{01}} = \frac{\lambda_1^T + \lambda_2^T}{\lambda_1^C + \lambda_2^C}, \qquad e^{\beta_{02}} = \frac{\lambda_3^T}{\lambda_3^C}$$

Combination of Initial Models for PFS and OS



- assumption of partial compliance in treatment arm with
  $\tau_1 = p_1 \cdot T_{PFS}$ time on treatment until progression
  $\tau_2 = p_2 \cdot T_1$ time on treatment between progression and death
- RPSFTM is $U = \int_0^{\tau_1} \mathrm{e}^{\beta_{01}} \,\mathrm{d}t + \int_{\tau_1}^{T_0} \,\mathrm{d}t + \int_0^{\tau_2} \mathrm{e}^{\beta_{02}} \,\mathrm{d}t + \int_{\tau_2}^{T_1} \,\mathrm{d}t$

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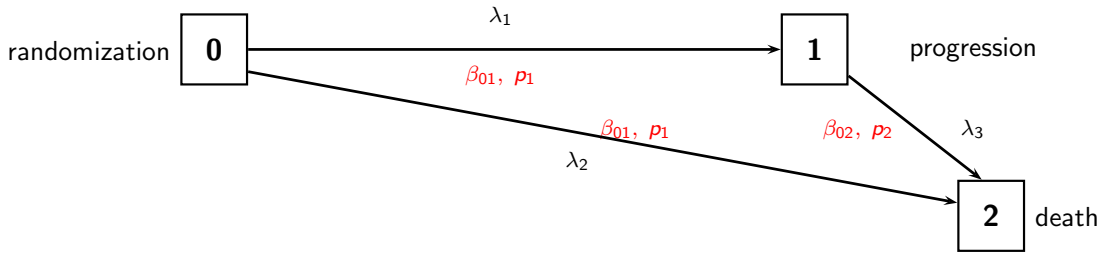

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- distribution of OS under partial compliance is given by

$$F_{T_{OS}}(t) = 1 - \frac{\lambda_1^P}{\lambda_1^P + \lambda_2^P - \lambda_3^P}\,\mathrm{e}^{-\lambda_3^P t} + \frac{\lambda_3^P - \lambda_2^P}{\lambda_1^P + \lambda_2^P - \lambda_3^P}\,\mathrm{e}^{-(\lambda_1^P + \lambda_2^P)t}$$

with $\lambda_1^P = (1-p_1)\lambda_1^C + p_1\lambda_1^T$, $\lambda_2^P = (1-p_1)\lambda_2^C + p_1\lambda_2^T$, $\lambda_3^P = (1-p_2)\lambda_3^C + p_2\lambda_3^T$

Estimation of Treatment Effect

- **G-Estimation**
  - grid search over sequence of clinically relevant values β
  - test for equality of baseline survival time distributions via log-rank statistic $G(\beta)$
  - estimate is given by $\hat{\beta} = argmin_{\beta}|G(\beta)|$
- for n-dimensional setting, with $n \geq 2$:
  - grid search
  - Nelder-Mead algorithm

Simulation Studies

Estimation for PFS alone:

True effect β_0	p	$\hat{\beta}$	MSE
$\log(1) = 0$	100%	0.0055	0.0039
	75%	0.0039	0.0071
	50%	-0.0027	0.0163
$\log(0.5) = -0.6931$	100%	-0.6862	0.0040
	75%	-0.6936	0.0612
	50%	-0.6957	0.2034
$\log(1/3) = -1.0986$	100%	-1.0949	0.0041
	75%	-1.0927	0.1757
	50%	-1.1105	0.5629

G-Estimation:

- N=1000 patients, 1 : 1 randomization
- 1000 runs
- grid search from -2 to 1, step size 0.01

- estimate $\hat{\beta}$ approximates true value β_0 very well
- absolute difference of estimate and true value less than 0.01 (stepsize of the grid search)
- estimation unaffected by non-compliances
- larger mean squared errors of $\hat{\beta}$ with rising non-compliances

Simulation Studies

Estimation for PFS and OS:

True Effect		Compliance Rate		Estimated Effect		Mean sqaured error	
β_{01}	β_{02}	p_1	p_2	$\hat{\beta}_{01}$	$\hat{\beta}_{02}$	$MSE(\hat{\beta}_{01})$	$MSE(\hat{\beta}_{02})$
log(0.5)	log(1)	100%	100%	-0.6829	-0.0168	0.0246	0.0161
		100%	75%	-0.6842	-0.0325	0.0224	0.0271
		75%	100%	-0.6742	-0.0211	0.0506	0.0141
		75%	75%	-0.6817	-0.0292	0.0502	0.0226
log(0.5)	log(0.5)	100%	100%	-0.6948	-0.7060	0.0266	0.5137
		100%	75%	-0.6909	-0.7233	0.0252	0.5652
		75%	100%	-0.6972	-0.7093	0.0769	0.5187
		75%	75%	-0.7101	-0.7174	0.0726	0.5551

G-Estimation:

- N=1000 patients, 1 : 1 randomization
- 1000 runs
- grid search from -2 to 1 for β_{01} and from $\beta_{01} - 1$ to $\beta_{01} + 1$ for β_{02},
- step size 0.1

- not as precise estimates as in one-parameter setting for PFS
- estimates of $\hat{\beta}_{02}$ are not as precise as those of $\hat{\beta}_{01}$
- Nelder-Mead algorithm saves computing time but gives less precise estimates than the grid search

Real Data

- data from a non-small-cell lung cancer trial:

Trial arm	Number of patients	Number of progressions	Median PFS time [days]	Number of deaths	Median OS time [days]
Placebo	137	136	29	84	302
Treatment	263	248	85	163	298
Total	400	384	58	247	300

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- hazard ratio for placebo vs. treatment arm
  - via Cox-model
    - for OS: 1.043 (0.801, 1.358)
    - for PFS: 0.355 (0.285, 0.442)
  - via one-parameter RPSFTM
    - for OS: 1.051 (0.7866, 1.448)
    - for PFS: 0.395 (0.320, 0.472)
- so far used approaches failed to explain the different effect of the treatment on PFS and OS

Real Data

- Trial Design:
  - until progression: placebo or test treatment
  - after progression: subsequent therapy (of same substance class as test treatment) in both study arms
- Modelling Approach:
  two-parameter RPSFTM with varying compliance rates
  - until progression: assumption of full compliance to test treatment in treatment group
  - after progression: compliance to subsequent therapy in both treatment arms

Assumed compliance p_2		Hazard Ratio for	
treatment arm	control arm	PFS	OS
0.4	0.6	0.517	0.357
0.3	0.7	0.387	0.449
0.2	0.8	0.262	0.468
0.6	0.7	0.538	0.310

Summary

- Combination of three-state model with RPSFTM enables to adjust for confounding effects due to
  - subsequent treatment after progression
  - crossin / crossover
  - non-compliances in treatment arm
- Estimation of separate treatment effects before and after progression is possible

- **Outlook**
  - a model for random fraction of non-compliances
  - suspending the assumption of identical progression rates
  - extension to a four-state model with a transient state 'responded' (e.g. for hematologic indications)

For Further Reading

- Fleischer F, Gaschler-Markefski B, Bluhmki E. 2009. *A statistical model for the dependence between progression-free survival and overall survival*. Statistics in Medicine 28 (21): 2669-2686
- Robins J M, Tsiatis A A. 1991. *Correcting for non-compliance in randomized trials using rank preserving structural failure time models*. Communications in Statistics; **20**: 2609-2631.
- Robins J M, Tsiatis A A. 1992. *Semiparametric estimation of an accelerated failure time model with time-dependent covariates*. Biometrika; **79** (2): 311-319.
- Korhonen P A, Laird N M, Palmgren J. 1999. *Correcting for non-compliance in randomized trials: an application to the ATBC study*. Statistics in Medicine **18**, 2879–2897