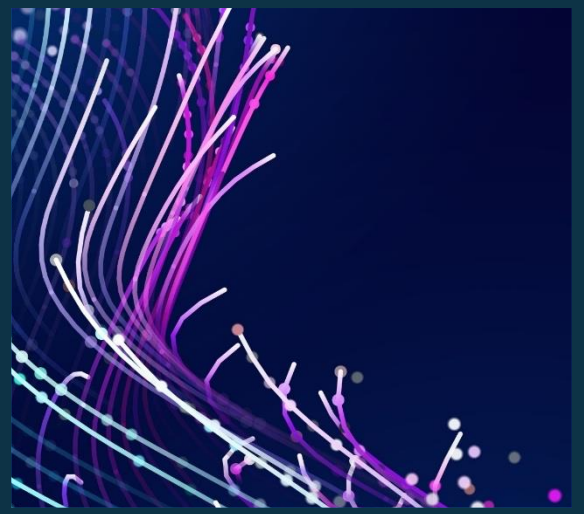


Illustrating treatment switching using Rank preserving structural failure time model in Oncology study

Swarupa Changan

For PHUSE APAC Connect 2026

20FEB2026

Abstract

In many randomized clinical trials, where survival is a key endpoint, subjects are usually intended to be on their assigned treatment until loss of clinical improvement or death. In oncology trials, the crossover from the control to the experimental treatment is reasonable when disease progression is observed or any other clinical criteria is noticed —a process known as *treatment switching*.

Traditional Intent-to-treat analyses that ignore such crossover which can underestimate the true effect of the experimental treatment on overall survival. To address this, we have the novel strategic model the **Rank-preserving structural failure time model (RPSFTM),**which effectively corrects the impact of crossover, and this method is used to estimate counterfactual survival—what would have occurred had patients not switched.

RPSFTM adjusts the effects of treatment switching by modeling, what the survival times of patients who switched treatments would have been if they had remained on the control treatment.

Motivation

1. Treatment Switching Dilutes ITT

- In oncology, patients in the **control arm** are often allowed to **cross over** to the experimental treatment at disease progression (for ethical reasons).
- While this is good for patients, it causes problems for analysis:
  - **ITT (intention-to-treat)** compares arms as randomized, but many control patients actually receive the experimental **ITT (intention-to-treat)** drug later.
  - This **biases the hazard ratio toward the null** (underestimates treatment benefit).

2. Naïve Analyses Don't Solve It

- **Per-protocol analysis** (exclude switchers) → breaks randomization, introduces selection bias.
- **Censor at switch** → informative censoring (patients who live longer are more likely to switch).
- Neither gives unbiased estimates of the treatment effect.

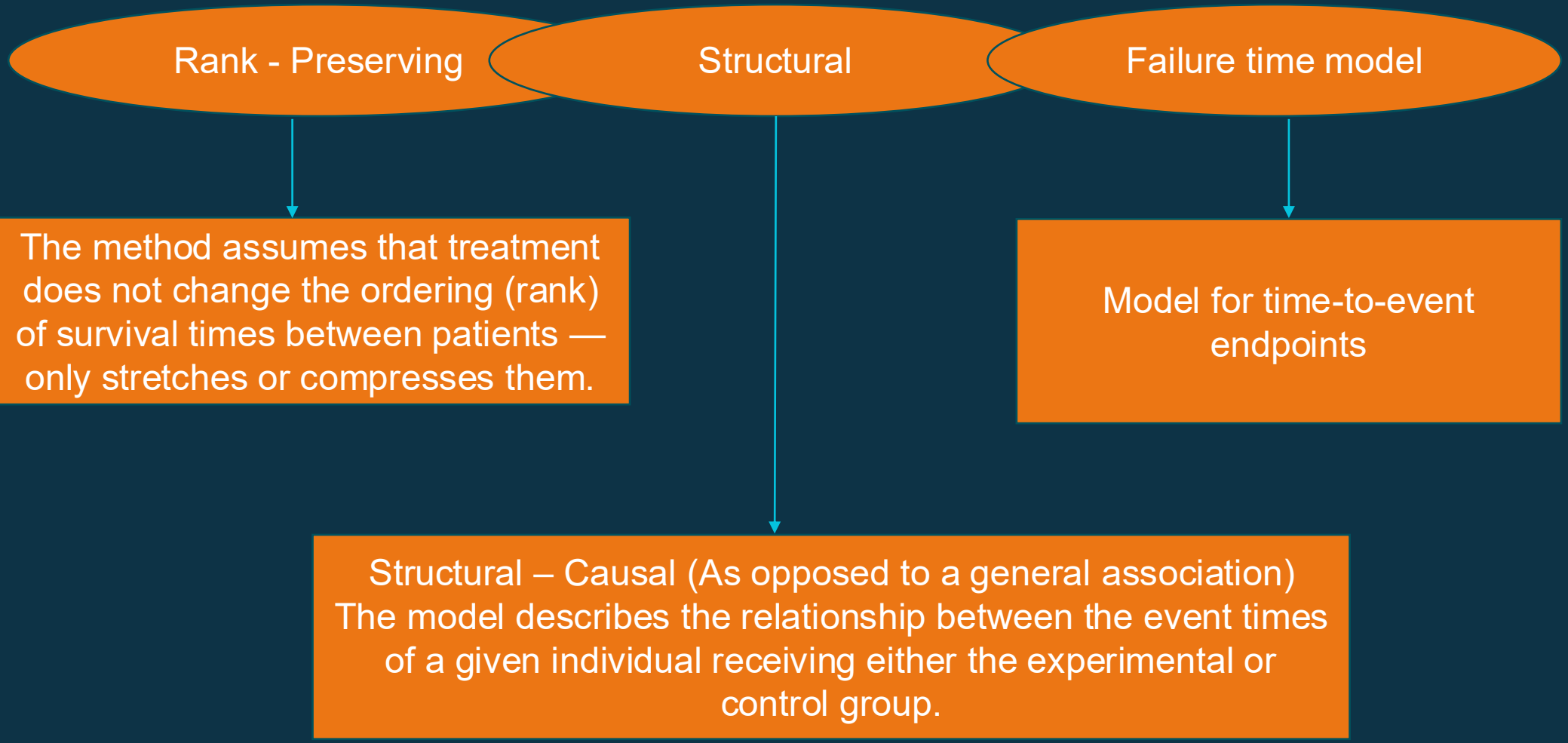
3. Need a Causal Method

- We want to know:
- "What would OS look like **if no patient in the control arm had switched** to the experimental drug?"
- To answer, we need a **causal framework** that:
  - Uses **randomization** as the instrumental variable.
  - Adjusts observed survival times to create **counterfactual times** (as if switching hadn't occurred).

What is RPSFTM??

- The **Rank Preserving Structural Failure Time model (RPSFTM)** is a causal inference method developed to estimate the treatment effect in randomized controlled trials where patients in the control arm are allowed to **switch to the experimental treatment** after disease progression (or for ethical reasons).
- This switching makes traditional survival analysis biased, because the control group ends up partially receiving the treatment.
- RPSFT helps “reconstruct” what survival times would have looked like **if no switching had occurred**, while preserving the **rank order** of failure times.

Rank preserving structural failure time model



Assumptions and Definitions

Assumptions: RPSFTM uses a different modelling approach based on randomization and hence there are no barriers in terms of switching proportions to use of this method. The key assumption of this model is that there is a common treatment effect, i.e. that the effect of treatment is the same whether it is given at randomization or at the point of disease progression.

Defining time on treatment: The switch treatment effect duration in these analyses can be assumed to last from first dose of experimental therapy until death/censoring ("treatment group" approach) or only on the days/cycles the subject receives experimental therapy ("on-treatment" approach). The treatment group approach will be used as the primary analysis, with the on-treatment approach. This is because given the mode of action, the effect of treatment is not expected to cease immediately following the final administration.

The RPSFT model structure

- The key assumption of this model is that there is a common treatment effect, i.e. that the effect of treatment is the same whether it is given at randomization or at the point of disease progression.
- The RPSFTM model estimates, for each patient, the counterfactual survival time in the absence of active treatment, and an active treatment effect that extends the survival time whilst the patient is on treatment.
- It is structured as follows.
  - Patient *i*
  - Observed time on active treatment T_i^{on}(=0 for control patients that do not switch)
  - Observed time off active treatment T_i^{off}
  - Observed survival time $T_i^{obs} = T_i^{off} + T_i^{on}$
  - Counterfactual survival time in the absence of active treatment $T_i(0)$
- Counterfactual and observed survival times are related through a treatment effect Ψ as follows:

$$T_i(0) = T_i^{off} + e^{\Psi} T_i^{on} \quad \ldots\ldots (1)$$

- e^{Ψ} is sometimes referred to as an acceleration factor, as it speeds up remaining life.
- The common treatment effect assumption comes from Ψ being identical for all patients.
- In a tipping point sensitivity analysis to assess the effect of reducing the effect in switchers compared to those randomized to treatment, Ψ is replaced with $s_i\Psi$ where s_i =1 for those randomized to experimental and s_i <1 for switchers.

RPSFT Model – estimate the acceleration factor

- The acceleration factor will be estimated via G-estimation using a grid search for Ψ with a step size of 0.01, with the same test statistic as the primary ITT analysis (log-rank test).
- G-estimation works in the following way:
  1. Select a value of Ψ
  2. Compute $T_i(0, y) = T_i^{off} + e^{\Psi} T_i^{on}$ for each patient *i* across both treatment groups
  3. Test the hypothesis of independent $T_i(0, \Psi)$ across treatment groups by calculating the test statistic Z(Ψ) for your chosen test
  4. Repeat for a range of values of Ψ

The chosen value of Ψ is the one that satisfies Z(Ψ) =0

- Model diagnostic checks will include plotting Z(Ψ) against Ψ to check monotonicity (i.e. a unique solution) and producing KM curves of counterfactual survival on both arms to check for similarity of distributions.

RPSFT Model –Compare switch-adjusted survival between arms

- For each patient, we observe T_i^{off} and T_i^{on}, and can model $T_i(0)$ using our estimate of Ψ and equation (1).

- The adjusted survival time for comparator arm patients in the absence of switching is therefore set as:
  - Observed data (=$T_i\ (0)$) for patients who did not switch
  - Modelled $T_i(0)$ for patients who switched
- A Kaplan-Meier curve of adjusted survival times and associated medians will be presented, along with the hazard ratio and two-sided 95% CIs.

For the RPSFT model, the main analysis has used the “treatment group” approach to defining time on Treatment group A and will not apply re-censoring. Kaplan Meier curves are produced for the observed survival in the treatment arm and the adjusted survival in the absence of switching in the control arm. The number of events and the medians from the KM curves provides you better approach for concluding the results.

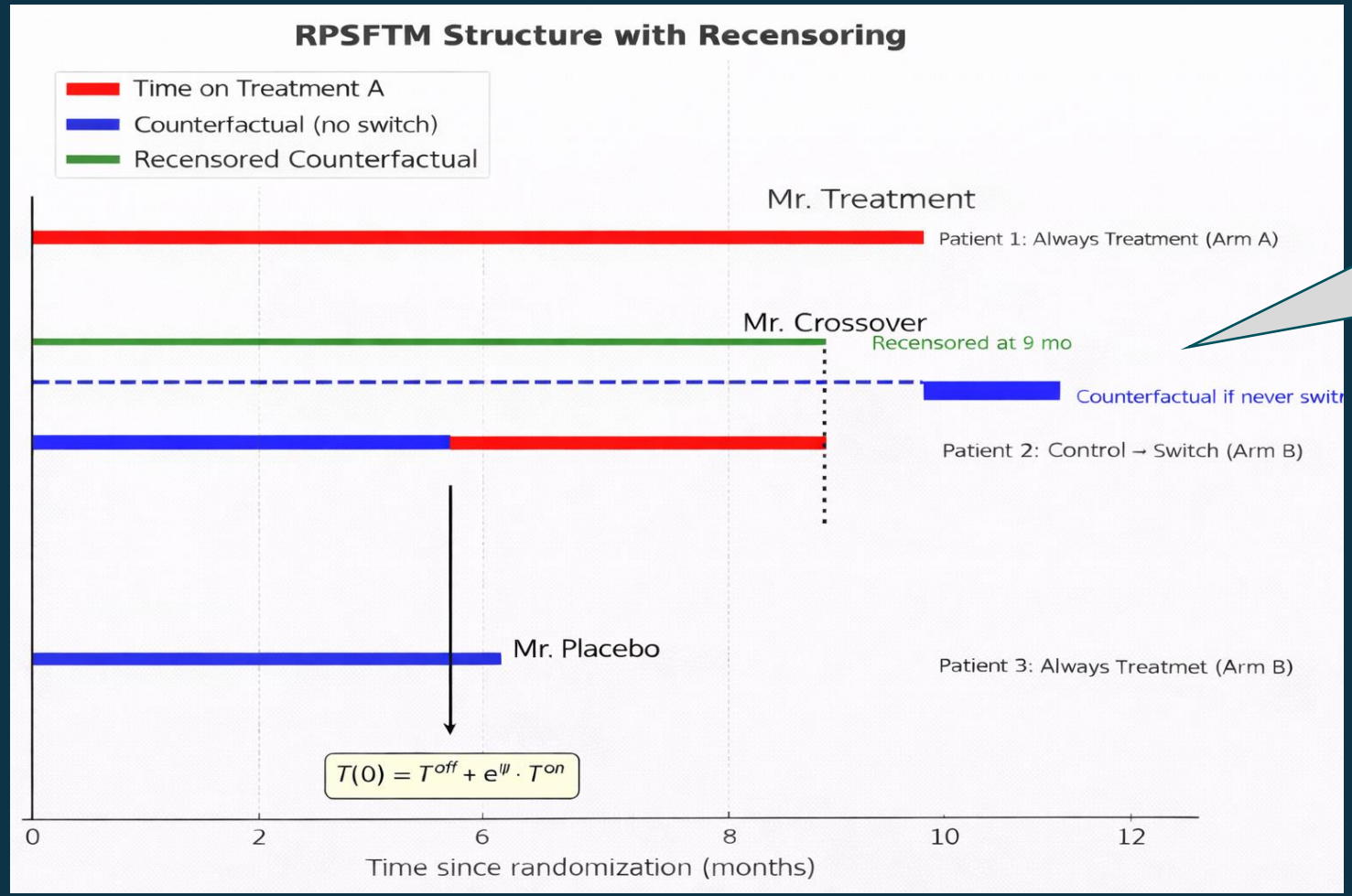
Recensoring

- In standard RPSFTM analysis, switchers often have shorter censoring times and different outcomes, introducing potential informative censoring and bias. Re-censoring addresses this by applying a consistent censoring rule to all patients, breaking the link between switching status and censoring time.
- After applying the treatment effect (Ψ), observed survival times are transformed into counterfactual times (U_i), during which previously uninformative censoring on the original time scale (T_i) may become informative, potentially violating model assumptions and biasing survival estimates.
- Re-censoring ensures transformed censoring times don't exceed the original censoring times. Let C_i be the administrative censoring time for patient *i*. The counterfactual survival time is recensored at:

$$D_{\mathrm{i}}(\Psi) = \min(C_i\,,\, C_i\, e^{\Psi})$$

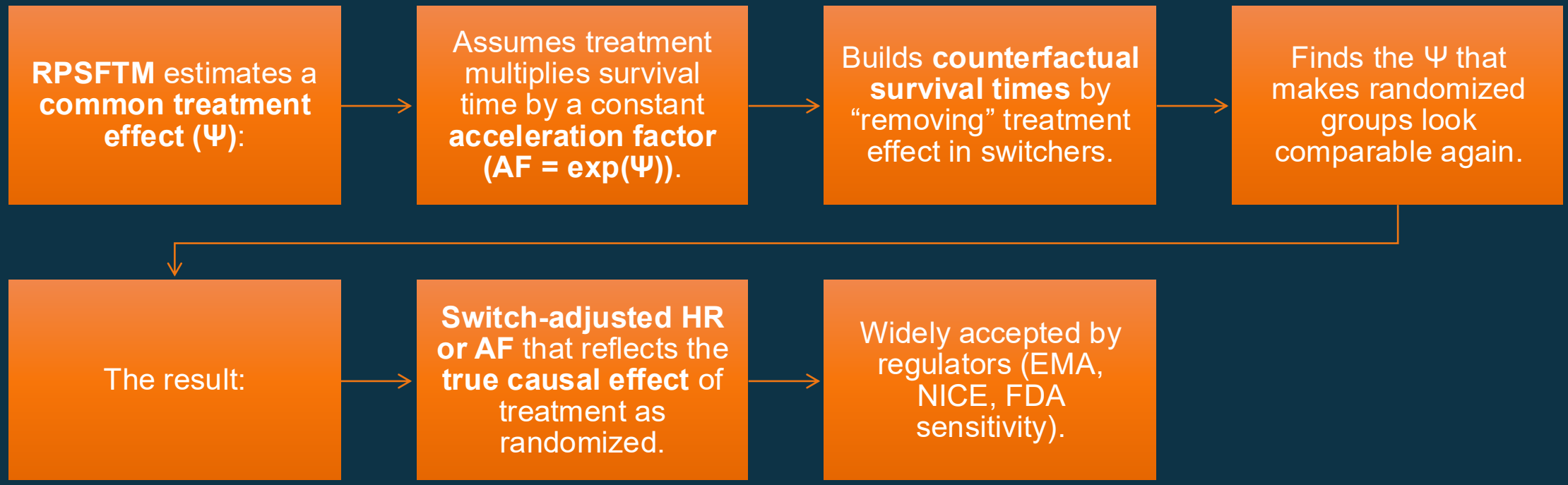
- If treatment is beneficial, then $D_{\mathrm{i}}(\Psi) < C_i$, leading to **shorter censoring times**. If $D_{\mathrm{i}}(\Psi) < U_i$, the survival time is truncated and the event is marked as censored.
- This ensures censoring is independent of switch status, reducing informative censoring bias.

RPSFTM Structure: Observed vs Counterfactual Survival



This diagram illustrates**: Mr. Crossover** switches from Control to Treatment A, and a counterfactual survival time is estimated assuming no switch; since it exceeds observed follow-up, recensoring is applied to avoid bias, while **Mr. Treatment** and **Mr. Placebo** remain on their assigned arms.

RPSFTM Provides the Solution



How RPSFTM works

Standard intention-to-treat (ITT) analysis can underestimate the true treatment effect when crossover occurs. The RPSFTM addresses this by adjusting for the crossover using a causal modeling approach based on g-estimation.

- **Acceleration Factor (ψ):** The model estimates a single parameter, the acceleration factor (ψ), which represents the multiplicative effect of the experimental treatment on a patient's survival time.
- **Counter-factual survival times**: Using ψ, the model constructs "counter-factual" survival times for patients who switched treatments, estimating what their survival would have been had they remained on their original randomized treatment.
- **Balancing Kaplan-Meier curves**: A g-estimation procedure finds the value of ψ that statistically balances the counter-factual survival curves of the two randomized groups. This is typically done by finding the ψ that makes a test statistic (e.g., a log-rank test statistic) equal to zero.
- **Recensoring**: Since standard censoring can become informative on the counter-factual time scale, a recensoring procedure may also be implemented as part of the model.

Implementing the RPSFTM in SAS is not a built-in function and requires a manual, macro-based approach. The purpose of RPSFTM is to adjust for the bias in survival outcomes caused by treatment switching, where patients in the control group cross over to receive the experimental treatment.

Case Study

Overall Survival (OS) is defined as the time from randomization to death due to any cause. Patients who have not died and withdraw from the study, or are otherwise lost to follow-up, will be censored at the time of study withdrawal. Patients still in the study who have not died will be censored at the last available contact. This study allows patients in the Treatment group B to cross-over to the Treatment group A at the time of first progression. In consequence, different clinical questions of interest can be formulated:

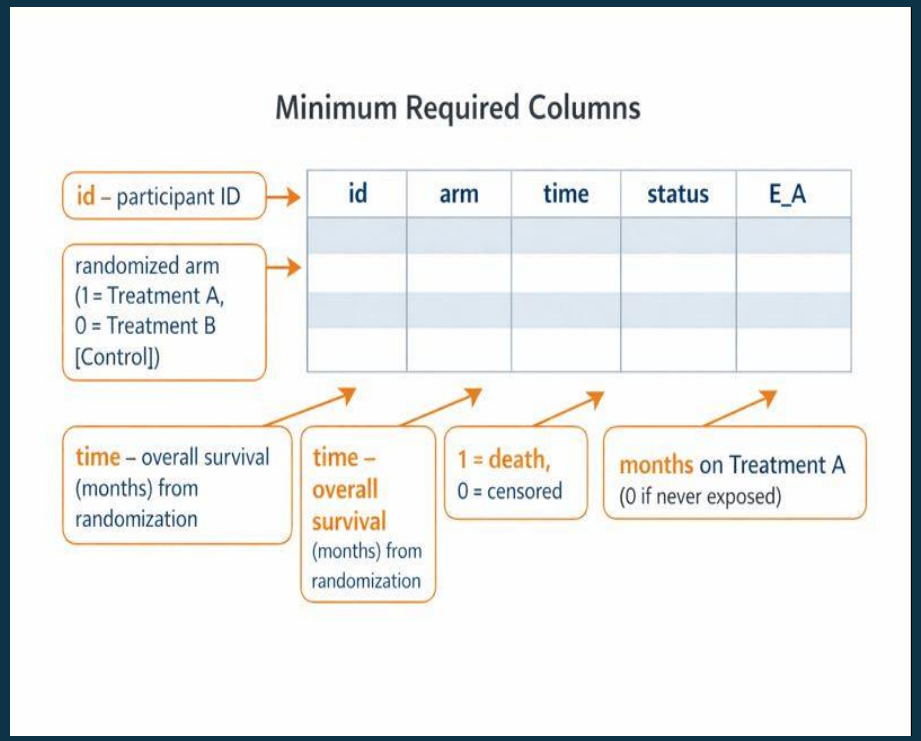
Study sample: 40 patients (21 on Treatment A, 19 on Treatment B i.e. Control).

- The effect on OS of the different treatment policies of initiating Treatment group A at randomization vs initiating Treatment group B with potential crossover to Treatment group A at time of radiographic progression
- The effect on OS that is attributable to the randomized treatments, accounting for the effect of crossover in the control arm in our case it is Treatment B.

For us, the second question is of more interest, as the estimation of the hazard ratio from the ITT analysis will be biased. To account for crossover and create unbiased estimates of the true hazard ratio in the absence of crossover treatment the Rank-Preserving Structural Failure Time Model (RPSFTM) is used.

Data Requirements for RPSFTM:

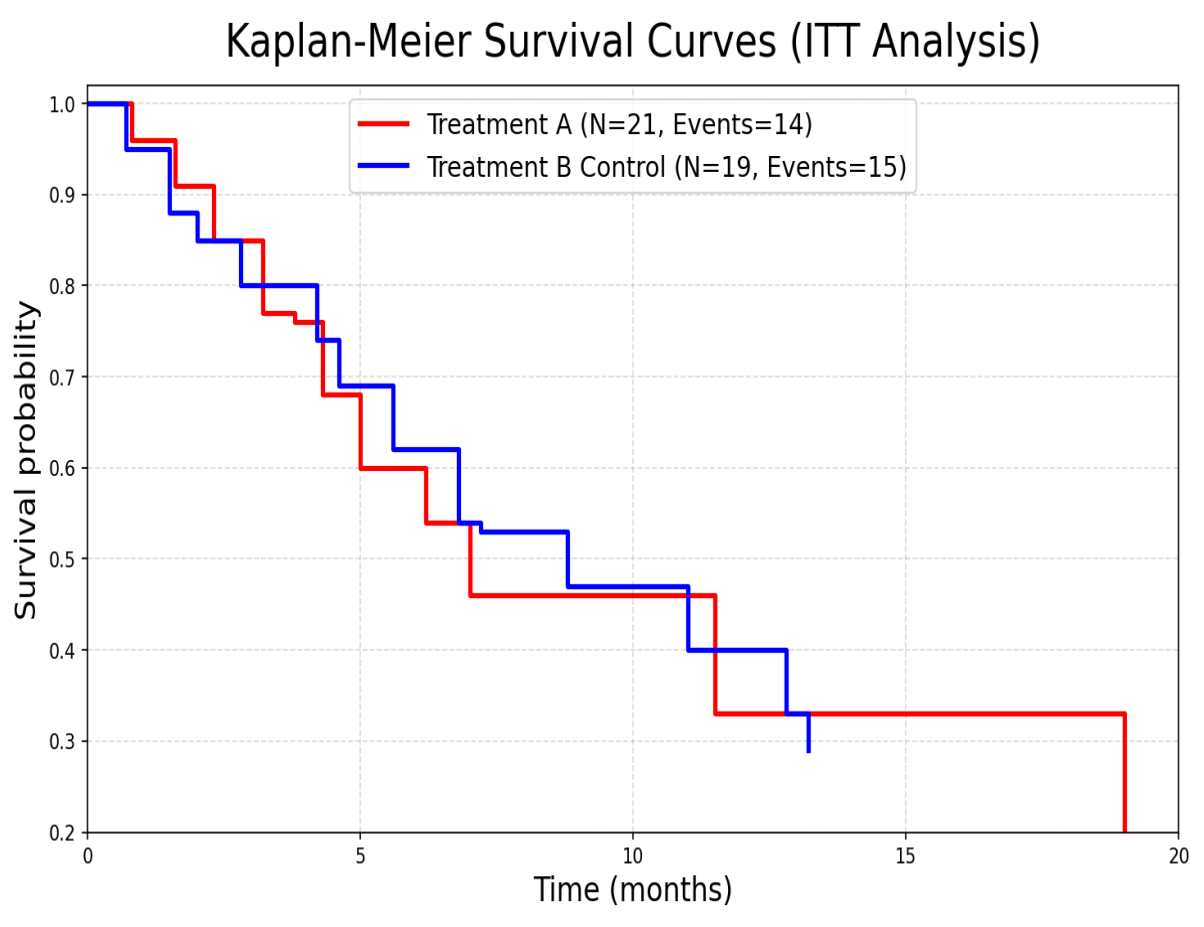
- **Minimum Required Columns**
  - id — participant ID
  - arm — randomized arm (1 = Treatment A, 0 = Treatment B [Control])
  - time — overall survival (months) from randomization
  - status — 1=death, 0=censored
  - E_A — months on Treatment A (0 if never exposed)
- **Helpful QC Columns**
  - rand_date — randomization date
  - prog_date — progression date
  - start_A / stop_A — start/stop timestamps of Treatment A
  - last_contact — last known alive / follow-up date
- **Key Notes**
  - Ensure 'time' and 'E_A' use the same time unit (months recommended)
  - Do NOT censor at crossover for ITT analysis
  - E_A must be duration, not a 0/1 indicator
  - Use censor_time = 'recensor' in rpsftm()



Minimal R Code for RPSFTM

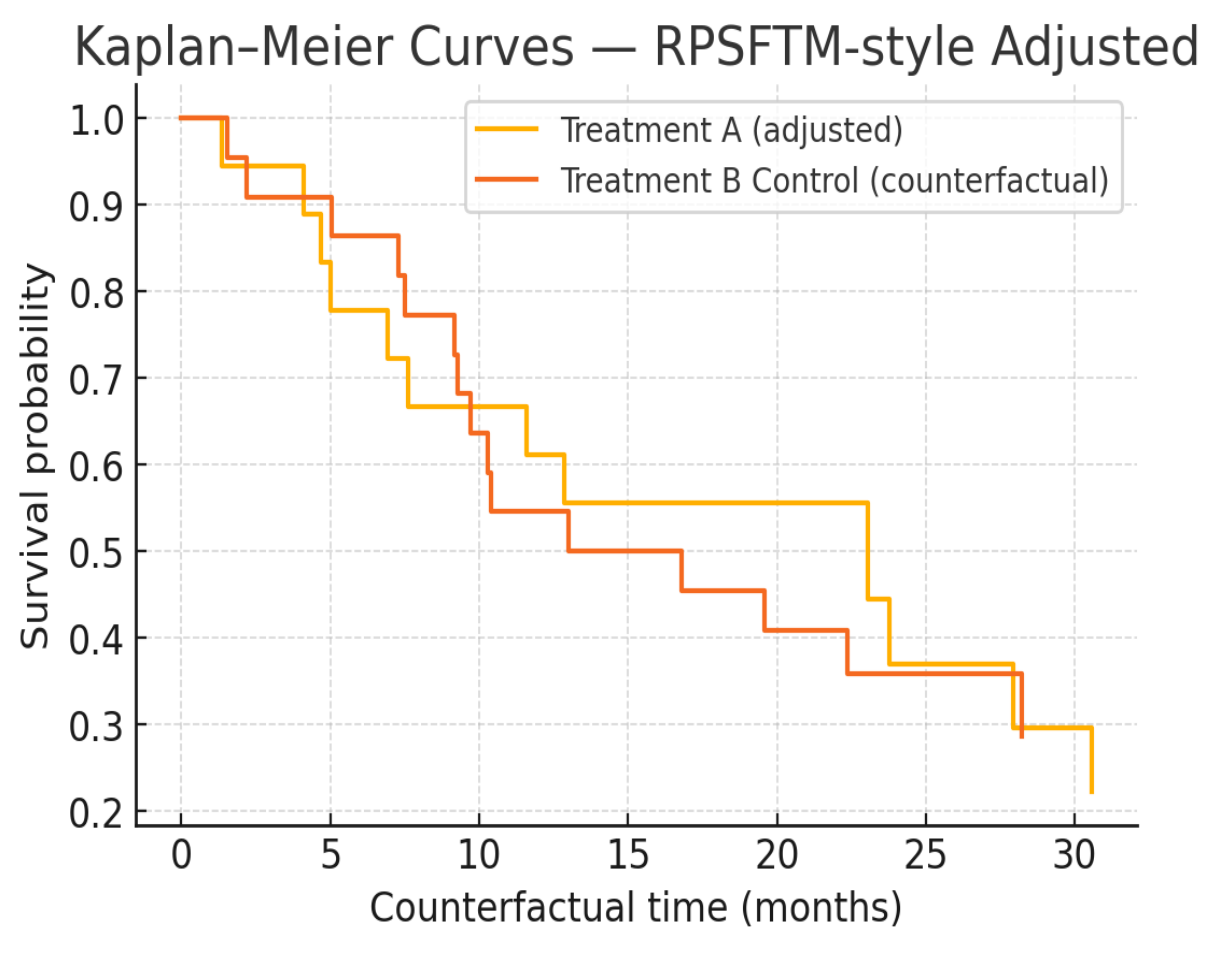
```
library(rpsftm)
library(survival)

dat <- read.csv("data.csv")

# ITT Cox HR
cox_itt <- coxph(Surv(time, status) ~ arm, data = dat)
summary(cox_itt)

# RPSFTM (treat = E_A months on Treatment A)
fit <- rpsftm(Surv(time, status) ~ rand(arm),
              data = dat,
              treat = dat$E_A,
              censor_time = "recensor",
              method = "logrank")
summary(fit)

# Counterfactual reconstruction + adjusted HR
dat_cf <- reconstruct(fit)
cox_adj <- coxph(Surv(cf_time, cf_status) ~ arm, data = dat_cf)
summary(cox_adj)
```

Kaplan–Meier Curves — ITT Analysis



- Treatment A (21 patients) vs Control (19 patients). About 60% of Control patients crossed over to Treatment A.
- Median OS: 14.5 months for Treatment A vs 13.0 months for Control.
- At 12 months, survival probability is ~60% in both groups, and the curves overlap.
- Curves overlap because Control patients who switched to Treatment A improved survival.
- Interpretation: ITT reflects the treatment policy of allowing crossover. Control patients benefit from switching, masking the true effect of Treatment A.
- Takeaway: ITT underestimates the biological effect of Treatment A.

Kaplan–Meier Curves — RPSFTM Adjusted



- Study sample: same 40 patients (21 on Treatment A, 19 on Control).
- Treatment A median OS is 23.0 months; Control (counterfactual, assuming no crossover) median OS is 13.0 months.
- At 18 months, survival probability ~55% for Treatment A vs ~30% for Control.
- Clear separation appears after adjusting for crossover bias.
- Interpretation: RPSFTM reconstructs what Control outcomes would have looked like without crossover. This shows the causal treatment effect.
- Takeaway: Treatment A improves survival by ~9–10 months compared to Control, demonstrating a clinically meaningful benefit.

Results

Analysis	Median OS(months)	Survival Probability	Hazard Ratio	95% CI	p-value
ITT(Unadjusted, with crossover)	Treatment A: 14.5 Treatment B:13	12 month survival~60% in both arms	0.81	(0.46-1.44)	0.47
RPSFTM Adjusted (Counterfactual Control)	Treatment A: 23.0 Treatment B:13	18 month survival:55%(A) vs 30% (B)	0.49	(0.29-0.81)	0.006

Interpretation: For ITT we can see Curves overlap; cross over masks the true benefit. For RPSFTM Adjusted we see clear benefit Treatment A improves OS by ~9–10 months compared to Control

Interpretation/Conclusions

ITT Analysis

- ITT analysis answers: *"What is the effect of starting Treatment A at randomization vs starting on Control, where crossover is allowed?"*
- Because many Control patients switched to Treatment A, their outcomes improved, **diluting the difference.**
- For Cox analysis: • ITT analysis (HR = 0.81, p = 0.47) shows no statistically significant difference, because crossover in the Control arm diluted the treatment effect.

Conclusion: ITT underestimates the true effect of Treatment A — it reflects a "treatment policy" comparison rather than the **biological effect** of Treatment A.

RPSFTM Analysis (Causal Question):

- RPSFTM estimates *"What would the Control group's OS have looked like if they had never crossed over to Treatment A?"*
- By "blipping down" the crossover survival time, RPSFTM reconstructs counterfactual survival and re-censors follow-up where necessary.
- This provides an unbiased **causal estimate** of Treatment A's effect, independent of switching.
- RPSFTM-adjusted analysis (HR = 0.49, p = 0.006) shows a statistically significant 51% reduction in risk of death for Treatment A compared with Control (counterfactual, no crossover).

Conclusion: After adjustment, Treatment A demonstrates a **clinically and statistically meaningful survival benefit**.

Key Message

- ITT analysis answers a policy question but may underestimate biological treatment effects when crossover is present.
- RPSFTM corrects for crossover bias and reveals the true causal effect on OS. Hence, ITT answers the policy question (real-world impact if switching is allowed), while RPSFTM addresses the causal effect question (the true effect of Treatment A vs never receiving it).
- A HR to be produced to compare the observed and adjusted control survival from a Cox analysis as per the ITT analysis in this case it was Cox, any analysis according to your study or problem should be used.
- Achieving results for this method is complex using SAS, however it can be produced using R package, as it has the in-build procedure for modelling RPSFTM. We have used R package to estimate the results.
- Combining ITT and RPSFTM analyses provides a comprehensive and regulatorily aligned assessment of treatment benefit.Together, these analyses provide a complete picture:
  - ITT → pragmatic treatment policy outcome.
  - RPSFTM → unbiased causal treatment effect.
- Regulatory agencies (EMA, FDA, NICE) frequently request RPSFTM or IPCW in oncology trials with crossover, as ITT alone is not sufficient.

References

- **Rank-preserving structural failure time models** for survival data, Simon Bond, Annabel Allison
- An R Package for Rank Preserving Structural Failure Time Models Annabel Allison, Ian R White, Simon Bond
- 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, P Korhonen E Zuber, M Branson
- Robins JM, Tsiatis AA. Correcting for noncompliance in randomized trials using rank preserving structural failure time models. Communications in Statistics—Theory and Methods 1991; 20:2609–2631.
- European Medicines Agency, IHC (International Conference on Harmonisation) topic E3, Structure and Content of Clinical Study Reports, Step 5, Note for Guidance on Structure and Content of Clinical Study Reports (CPMP/ICH/137/95), July 1996
- International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Statistical Principles for Clinical Trials (E9), 5 February 1998.
- WHO Collaborating Center for International Drug Monitoring. WHO Drug Dictionary. June 2012 B Format edition. Uppsala, Sweden; 2008.

Thank you


Q
A