Paper AS18

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

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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 eventually 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.

Introduction

Overall Survival (OS) is widely regarded as a gold-standard endpoint in oncology clinical trials. In many randomized studies, patients assigned to the control arm are allowed to cross over to the experimental treatment upon disease progression. While ethically justified, such treatment switching complicates survival analysis because post-randomization treatment exposure differs from randomized assignment.

Under crossover, the ITT analysis answers a pragmatic “treatment policy” question: What is the effect of initiating Treatment A at randomization vs initiating Control when crossover to Treatment A is allowed? However, stakeholders often also need the causal “biological effect” estimand: What would OS have been if control patients had never switched to Treatment A? Addressing this causal question requires randomization-based methods that appropriately adjust for switching.

Now let’s see how this works:-

Method: RPSFTM Overview

1. Why Naïve Approaches Fail

Common alternatives to ITT analysis include:

- **Per-protocol analysis**, which excludes patients who switch treatments, breaking randomization and introducing selection bias.
- **Censoring at treatment switch**, which leads to informative censoring because patients who live longer are more likely to switch.

Neither approach provides an unbiased estimate of the causal treatment effect on OS. A randomization-based causal framework is therefore required.

2. Rank-Preserving Structural Failure Time Model (RPSFTM)

The RPSFTM is a causal inference method designed for randomized trials with treatment switching. The model assumes that treatment acts to accelerate or decelerate survival time without changing the rank order of failure times between patients. The treatment effect is summarized by a single acceleration factor, ψ.

Key features of RPSFTM include:

- Preservation of randomization as the instrumental variable
- Construction of counterfactual survival times representing outcomes had switching not occurred
- Use of g-estimation to identify the ψ value that balances counterfactual survival distributions between randomized arms
- Optional recensoring to maintain non-informative censoring on the counterfactual time scale.

- **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.

2.1 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 $T\_i\text{^}on$(=0 for control patients that do not switch)
  - Observed time off active treatment $T\_i\text{^}off$
  - Observed survival time $T\_i\text{^}obs = T\_i\text{^}off + T\_i\text{^}on$
  - 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:

$$T\_i\ (0) = T\_i\text{^}off + e\text{^"}\Psi\text{"}\ T\_i\text{^}on \quad \ldots\ldots\ (1)$$

- $e\text{^"}\Psi\text{"}$ 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.

2.2 Estimation of 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:
  - Select a value of Ψ

- Compute $T_i(0,y) = T_i^{off} + e^{\Psi} T_i^{on}$ for each patient *i* across both treatment groups
- Test the hypothesis of independent $T_i(0,\Psi)$ across treatment groups by calculating the test statistic Z(Ψ) for your chosen test
- 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.

2.3 Comparing 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.

2.4 Recensoring:

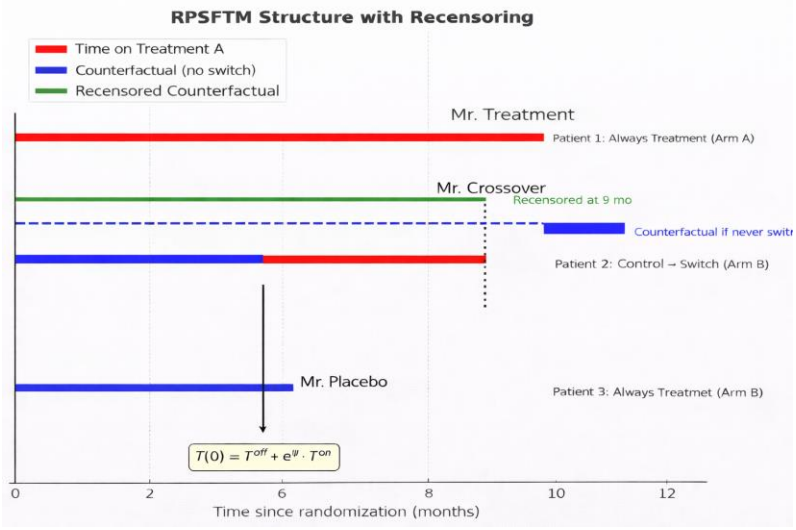
- In standard RPSFTM analysis, switchers often have shorter censoring times and different outcomes, introducing potential informative censoring and bias. Re-censoring addresses this by applying a consistent censoring rule to all patients, breaking the link between switching status and censoring time.
- 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:

$$D_i(\Psi) = \min(C_i, C_i e^{\Psi})$$

- If treatment is beneficial, then $D_i(\Psi) < C_i$, leading to **shorter censoring times**. If $D_i(\Psi) < U_i$, 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

Figure 1 :



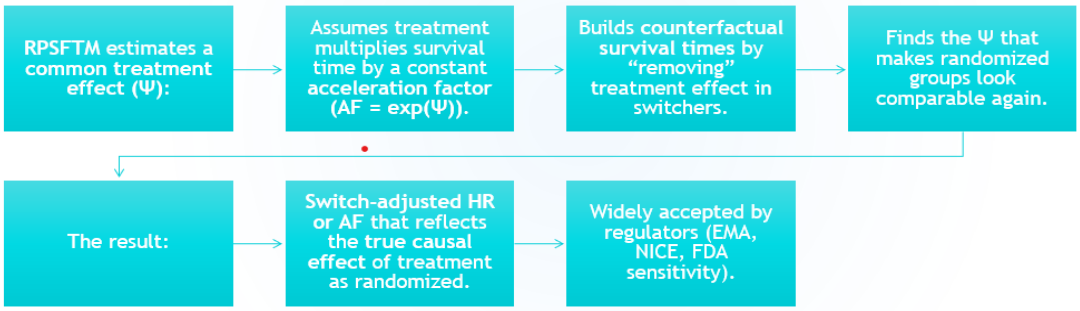
This Figure1, illustrates the RPSFTM adjustment process.

Mr. Crossover (Patient 2), initially on Control (blue), switches to Treatment A (red). The model estimates a counterfactual survival time (dashed blue), representing survival had no switch occurred. Because this counterfactual exceeds the observed follow-up (9 months), recensoring is applied (green bar) to truncate survival at the censoring time.

Mr. Treatment (Patient 1) remains on Treatment A throughout, while Mr. Placebo (Patient 3) remains on Control. Recensoring ensures counterfactual times do not exceed observed follow-up, preserving non-informative censoring and reducing bias. (green bar) to truncate survival at the censoring time.

RPSFTM Provides the Solution:

Chart 1 :



3. Case Study Description

3.1 Study Design

A simulated oncology study was used to illustrate the methodology:

- **Total sample size:** 40 patients
- **Treatment A:** 21 patients
- **Control (Treatment B):** 19 patients
- **Crossover:** Control patients allowed to cross over to Treatment A at first radiographic progression

3.2 Endpoint Definition

Overall Survival (OS) was defined as the time from randomization to death from any cause. Patients who were alive at last contact or withdrew from the study were censored at the time of last known follow-up.

a. Clinical Questions of Interest:

Two distinct estimands were considered:

1. **Policy estimands:** OS under a strategy of initiating Treatment A at randomization versus initiating Control with allowed crossover.
2. **Causal estimands (primary interest):** The effect on OS attributable to the randomized treatments, accounting for crossover in the control arm.

Because crossover occurs post-randomization, ITT analysis is expected to provide a biased estimate for the second question.

4. Data Structure and Requirements using R package:

The minimum dataset required for RPSFTM included:

- id – patient identifier
- arm – randomized treatment (1 = Treatment A, 0 = Control)
- time – OS time (months)
- status – event indicator (1 = death, 0 = censored)
- E_A – cumulative time on Treatment A (months)
  - Time variables were consistently measured in months i.e. Ensure 'time' and 'E_A' use the same time unit (months recommended)
  - Patients were **not censored at crossover** for ITT analysis.
  - E_A must be duration, not a 0/1 indicator

Using this method is R is much more easier when compared with SAS, as, R provides the RSFTM package easily.

5. Statistical Analysis Methods

5.1 ITT Analysis:

Below is the minimal R program to generate the results detailed R program is provided in the Appendix:

An ITT Cox proportional hazards model was fitted:

```
library(survival)
cox_itt <- coxph(Surv(time, status) ~ arm, data = dat)
summary(cox_itt)
```

Kaplan–Meier curves were generated to visualize OS by randomized arm for ITT analysis.

5.2 RPSFTM Analysis

The RPSFTM was implemented using the rpsftm method with R package (Version 4.5.1):

```
library(rpsftm)
fit <- rpsftm(
  Surv(time, status) ~ rand(arm),
  data        = dat,
  treat       = dat$E_A,
  censor_time = "recensor",
  method      = "logrank"
)
summary(fit)
```

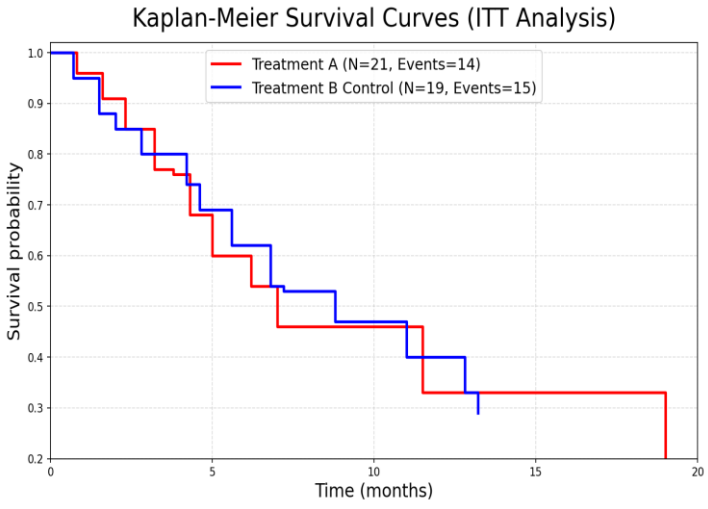
Counterfactual survival times were reconstructed and analyzed using a Cox model:

```
dat_cf <- reconstruct(fit)
cox_adj <- coxph(Surv(cf_time, cf_status) ~ arm, data = dat_cf)
summary(cox_adj)
```

6. Results:

6.1 ITT Results:

Figure 2:

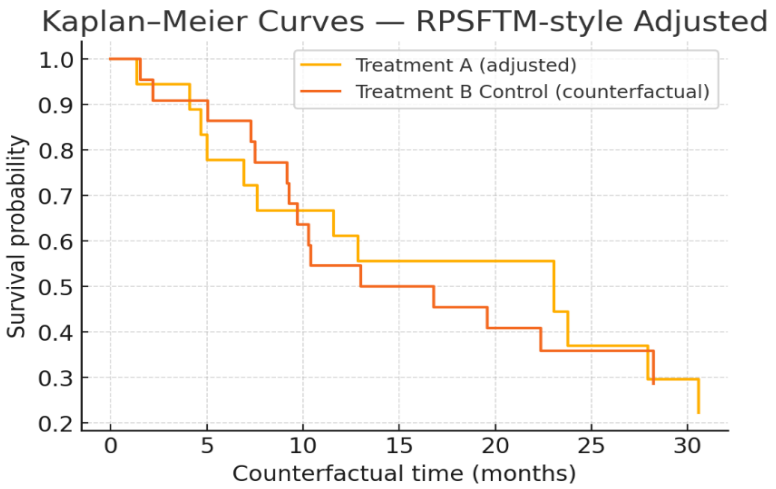


- Approximately **60% of control patients crossed over** to Treatment A.
- Median OS:
  - Treatment A: **14.5 months**
  - Control: **13.0 months**
- At 12 months, survival probability was approximately **60% in both arms**.
- Kaplan–Meier curves overlapped, reflecting dilution of treatment effect due to crossover.
- ITT Cox analysis showed no statistically significant difference (HR ≈ 0.81, p ≈ 0.47).

Interpretation:
The ITT analysis reflects the treatment policy of allowing crossover. Control patients benefited from switching, masking the true biological effect of Treatment A.

6.2 RPSFTM-Adjusted Results:

Figure 3:



- Counterfactual analysis assuming no crossover showed:
  - Median OS for Treatment A: **~23.0 months**
  - Median OS for Control: **~13.0 months**
- At 18 months, survival probability was approximately **55% for Treatment A vs 30% for Control**.
- RPSFTM-adjusted Cox analysis showed:
  - HR ≈ **0.49**
  - p ≈ **0.006**

Interpretation:
After adjusting for crossover, Treatment A demonstrated a clinically and statistically meaningful survival benefit of approximately **9–10 months**.

Note: 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.

Table 2:

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

Under RPSFTM adjustment, counterfactual control outcomes (assuming no crossover) separates clearly from Treatment A, demonstrating the causal treatment effect. In this example, the adjusted analysis corresponds to an estimated hazard ratio of approximately 0.49 ($p \approx 0.006$), consistent with a clinically meaningful survival advantage for Treatment A.

Discussion

This worked example highlights a common oncology challenge: ethically motivated crossover can mask treatment benefit under ITT. RPSFTM provides a randomization-based approach to estimate the causal effect in a no-switching scenario while preserving the core strength of randomized trials.

Because RPSFTM relies on the common treatment effect assumption and exposure definition, it is good practice to present ITT (policy estimand) and RPSFTM (causal estimand) together, supported by sensitivity analyses.

Conclusions:

- 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.

Software And Reproducibility

Analyses were implemented in R (R 4.5.1 or later recommended) using survival, survminer, and rpsftm. Exact package versions can be captured via sessionInfo() (included in Appendix).

APPENDIX: Full R Workflow

```
# ========================================================================
# PHUSE APAC 2026 Worked Example
# Treatment Switching Adjustment Using RPSFTM (Overall Survival)
# ========================================================================

# Install packages if needed (run once)
# install.packages(c("survival","survminer","rpsftm"))

library(survival)
library(survminer)
library(rpsftm)

# ------------------------------------------------------------------------
# 1) Read data
# ------------------------------------------------------------------------
dat <- read.csv("PHUSE_RPSFTM_Case_Study_Dataset.csv")

# Basic checks
table(dat$arm)                          # 21 in A, 19 in B
mean(subset(dat, arm=="B")$crossover)  # ~60% cross-over

# ------------------------------------------------------------------------
# 2) ITT Kaplan-Meier and Cox model
# ------------------------------------------------------------------------
surv_obj <- Surv(time = dat$os_time, event = dat$os_event)

fit_itt <- survfit(surv_obj ~ arm, data = dat)

# Medians and point estimates
summary(fit_itt)$table[,"median"]
summary(fit_itt, times = 12)$surv

# ITT Cox model
cox_itt <- coxph(surv_obj ~ arm, data = dat)
summary(cox_itt)

# ---- Figure 2: ITT KM curve ----
p1 <- ggsurvplot(
  fit_itt, data = dat,
  risk.table = TRUE,
  conf.int = FALSE,
  legend.title = "Randomized Arm",
  legend.labs = c("Treatment A","Control (B; crossover allowed)"),
  xlab = "Time since randomization (months)",
  ylab = "Overall Survival Probability",
  ggtheme = theme_bw()
)
p1$plot <- p1$plot + annotate("text", x = 12, y = 0.55,
                              label = "Curves overlap as Control\npatients switch to
Treatment A",
```

```
                              size = 3.5)
print(p1)
ggsave("Figure2_KM_ITT.png", p1$plot, width = 8, height = 6, dpi = 300)

# ------------------------------------------------------------------------
# 3) Define exposure time on Treatment A (E_A)
# ------------------------------------------------------------------------
# E_A = cumulative time on Treatment A (months)
dat$E_A <- with(dat, ifelse(
  arm == "A",
  os_time,                          # always on A
  ifelse(crossover == 1 & !is.na(prog_time),
         pmax(0, os_time - prog_time),  # time on A after switching
         0)
))

summary(dat$E_A)  # QC

# ------------------------------------------------------------------------
# 4) Fit RPSFTM (logrank g-estimation + recensoring)
# ------------------------------------------------------------------------
fit_rpsftm <- rpsftm(
  Surv(os_time, os_event) ~ rand(arm),
  data = dat,
  treat = dat$E_A,
  censor_time = "recensor",
  method = "logrank"
)
summary(fit_rpsftm)

# ------------------------------------------------------------------------
# 5) Reconstruct counterfactual survival and estimate adjusted HR
# ------------------------------------------------------------------------
dat_cf <- reconstruct(fit_rpsftm)

# Inspect names. rpsftm commonly returns cf_time and cf_status.
names(dat_cf)

cox_adj <- coxph(Surv(cf_time, cf_status) ~ arm, data = dat_cf)
summary(cox_adj)

# ---- Figure 3: RPSFTM-adjusted KM curve ----
fit_adj <- survfit(Surv(cf_time, cf_status) ~ arm, data = dat_cf)

p3 <- ggsurvplot(
  fit_adj, data = dat_cf,
  risk.table = TRUE,
  conf.int = FALSE,
  legend.title = "Arm",
  legend.labs = c("Treatment A (observed)","Control (counterfactual; no crossover)"),
  xlab = "Time since randomization (months)",
  ylab = "Overall Survival Probability",
  ggtheme = theme_bw()
)
p3$plot <- p3$plot + annotate("text", x = 18, y = 0.35,
```

```
                            label = "Clear separation after\nadjusting for
crossover",
                            size = 3.5)
print(p3)
ggsave("Figure3_RPSFTM_Adjusted.png", p3$plot, width = 8, height = 6, dpi = 300)

# ------------------------------------------------------------------------
# END
# ------------------------------------------------------------------------
```

References

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