Adjusting Overall Survival for Subsequent Therapies
Practical Insights into RPSFTM and IPCW

Mana Aizawa, Yosuke Fujii, Masatoshi Nakamura, Shigeyuki Toyoizumi and Shintaro Hiro
Pfizer R&D Japan

Background & Objective

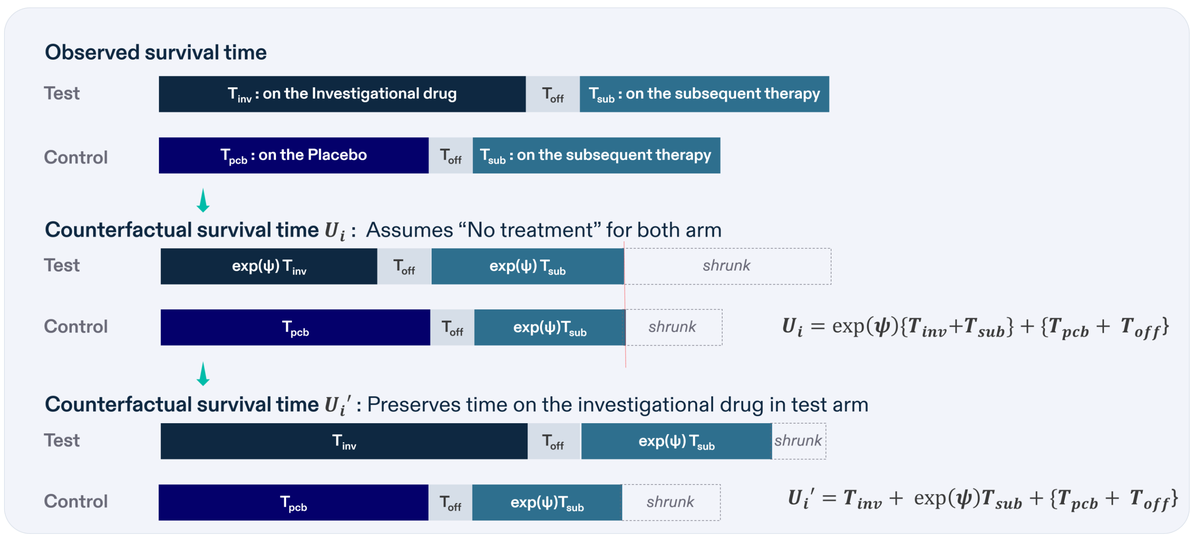
Overall survival (OS) is a key endpoint in oncology clinical trials for assessing efficacy and safety, but may be affected by subsequent therapy.
Analyses under a hypothetical strategy, such as assuming no subsequent therapy, may therefore be informative.
These statistical challenges have also attracted attention from regulatory authorities.
Complex methods, including RPSFTM and IPCW, can be used to address this hypothetical scenario.

Objective:
To apply RPSFTM and IPCW to clinical trial data to address the impact of subsequent therapy on OS and identify practical challenges.

Method

RPSFTM - Estimates survival without subsequent therapy –

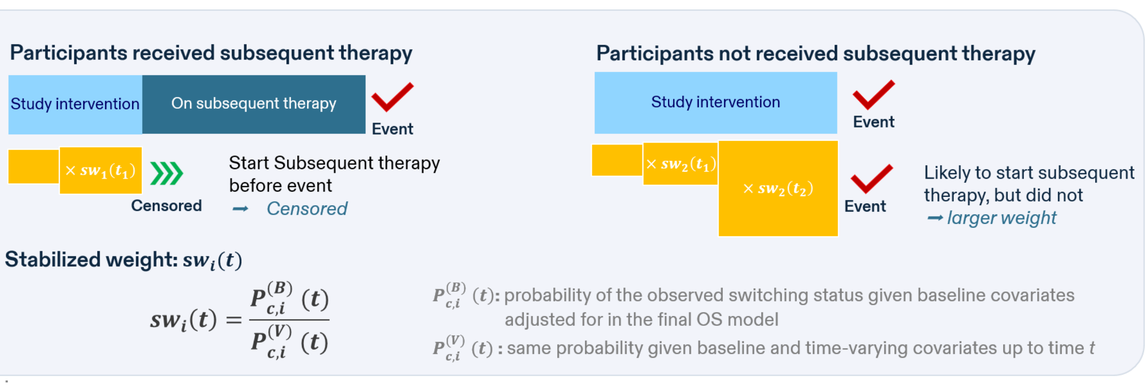
Key assumption: Common treatment effect
-same effect for all patients, regardless of treatment start time



In this work, we adjusted for the effects of subsequent therapy in both treatment arms by calculating counterfactual survival times, as illustrated above.

IPCW - Estimate OS in a weighted pseudo-population –

Key assumption: No unmeasured confounders
-all factors driving both switching/survival are measured



To account for time-varying covariates, the probability of initiating subsequent therapy can be estimated using pooled logistic regression or Cox regression models. In this work, we used pooled logistic regression model.

RPSFTM vs IPCW: Strengths and Limitations

RPSFTM	IPCW
Strength	**Strength**
• Randomization-based estimation for treatment switching • Robust to high switching rates • Limited data requirements	• Covariate-based adjustment for informative censoring • Adjusts for time-varying confounders • Flexible across treatment types
Limitations	**Limitations**
• Common (or constant) treatment effect • Uncertain suitability beyond crossover • Fitting difficulties (e.g., acceleration factors has multiple roots) • Little adjustment when HR is near 1 • Preserves ITT p-value (conservative) • Limitations of multi-parameter models	• Untestable assumption of no unmeasured confounders • Sensitivity to switching proportions • Highly dependent on data and model specification (data intensive, covariate issues, correct model specification) • Weights variability and interpretation • Not randomization-based

Application

Data

- Data from randomized oncology Ph3 clinical trial
  - Comparison : Investigational drug (Test) vs Placebo (Control)
  - Focus : Subgroup of interest within the trial population (n ≅ 230)
- Key findings in the subgroup
  - OS (Final analysis) : HR = 1.087 (95% CI: 0.763, 1.549)
  - Subsequent therapy: 37% vs 44% (Test vs Control)
  - Imbalances in several baseline prognostic factors
    → Adjusted for as stratification factors

Setting

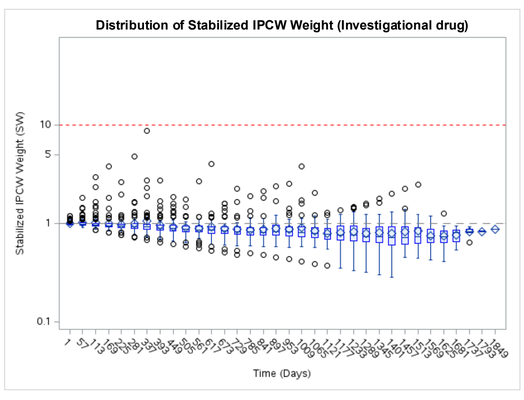
- RPSFTM
  Counterfactual survival times were derived assuming an equivalent treatment effect between the investigational drug and subsequent therapy.
- IPCW
  10 baseline and 6 post-baseline/time-varying covariates were considered. Covariates used as stratification factors were included in the numerator of the stabilized weights.

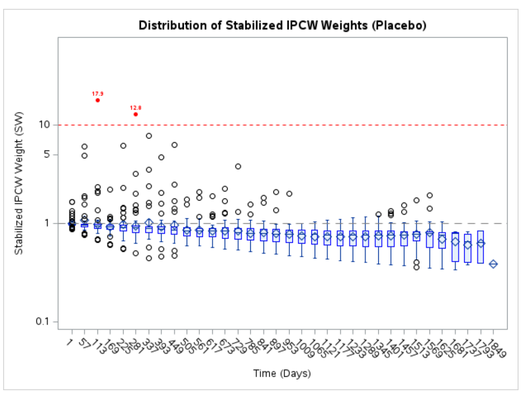
Results

Method	Stratified HR* (95% CI)
Unadjusted OS	0.927 (0.635, 1.355)
RPSFTM	0.954 (0.653, 1.394)
IPCW	0.879 (0.505, 1.529)

*Stratified factors: baseline prognostic factors with between-arm imbalances

- RPSFTM results are consistent with unadjusted results
  - Similar results without subsequent-therapy effects suggest limited impact ($\psi = -0.07$ (95% CI: $-0.64, 0.40$))
  - Caution: strong assumption of equal effects for investigational drug and subsequent therapy
- IPCW results are unstable
  - Subsequent-therapy model validity is difficult to assess
  - Interval-specific weights: increasing variability may destabilize adjusted OS





Practical considerations

- RPSFTM informed the response, but doubts remained about equal effects of active and subsequent treatments
- IPCW difficult model justification, unstable results and challenging interpretation
- Choose methods for scientific validity rather than favorable results
- Consistency across unadjusted and (multiple) adjusted analyses may support robustness

Future issues

- RPSFTM: Common treatment effect assumption
  - Drug-specific acceleration factors or effect parameters?
- IPCW: Implementation challenges
  - Covariate selection for the subsequent-therapy model
  - Patient profiles associated with large weights
- Interim analyses: How to address adjustment with immature OS data?

Reference

Watkins C, Kleine E, Miranda M, Bourmaud E, Doehring Q. Further Practical Guidance on Adjusting Time-To-Event Outcomes for Treatment Switching. Pharm Stat. 2025;24(4):e70019
Mosier B. Survival Methods for Crossover in Oncology Trials. PharmaSUG 2023 Conference Proceedings. 2023:Paper AP-191.