Adjusting Overall Survival for Patient Crossover

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Crossover Guidance

- When patients can change treatments at time of progression, analysis of overall survival (OS) can be complicated

- Methods for adjusting OS:
  - **Standard methods:** ITT analysis, exclude switch patients, censor at switch, time-varying covariates
  - **Structural Models**: estimate the hypothetical (counterfactual) survival times if crossover not occurred Rank Preserving Structural Failure Time models (**RPSFT**), Two-stage methods
  - **Censoring and Weighing:** censor patients at switch time, weight by how likely they are to switch Inverse Probability of Censoring Weighting (**IPCW**)
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- Limited guidance from regulatory: EMA released Q&A, NICE (not regulatory) has detailed guidance

- Adjustment methods are recommended as *supporting* or *sensitivity* analyses.

Regulatory Guidance Sources

- EMA Q&A:

https://www.ema.europa.eu/en/documents/scientific-guideline/question-answer-adjustment-cross-over-estimating-effects-oncology-trials_en.pdf

- NICE:

Latimer, Nicholas R., and Keith R. Abrams. "NICE DSU Technical Support Document 16: Adjusting survival time estimates in the presence of treatment switching." (2014): 18.

Methods to Account for Bias

- "Naïve Methods"
  - ITT analysis, exclude pts who switch, censor at time of switch, treatment as a time-varying covariate
- Structural Models
  - Model what time-to-event *would have been* with no switching (*counterfactual*)
  - Rank Preserving Structural Failure Time (**RPSFT**), Iterative Parameter Estimation (IPE), **two stage models**
- Weighted Models
  - Censor at switch, weight patients by how likely they are to switch treatment
  - Inverse probability of Censoring Weights (**IPCW**)

Intent to Treat (ITT) Analysis

- An ITT analysis will be required by protocol but has problems:
  - Treatment effect is diluted when post progression survival time is extended
    - Good for patients, bad for statistics
  - Patients with worse outcomes may switch at a higher rate

- Censoring at time of PD or dropping patients who switch is a common analysis but has drawbacks:
  - Decreases sample size and power
  - Prognostic balance from randomization/stratification is violated

ITT Analysis Sources

Lee, Young Jack, et al. "Analysis of clinical trials by treatment actually received: is it really an option?." *Statistics in medicine* 10.10 (1991): 1595-1605.

White, Ian R. "Uses and limitations of randomization-based efficacy estimators." *Statistical methods in medical research* 14.4 (2005): 327-347.

Counterfactual Survival Times

- Define the *counterfactual* survival time, U_i, as the survival time had the patient not received treatment

- **Assumption**: The distribution of U_i is the same for both arms
  - No "unmeasured confounding" conditional on baseline covariates
  - Treatment patients would have similar survival times as ctrl patients had they not received treatment.
  - No prognostic differences between arms

- We observe:
  - U_i for patients on the control arm
  - U_i until time of switch for patients who change treatment

Rank Preserving Structural Failure Time (RPSFT)

Partition time into:

Time to event = Time on control + time on treatment

$$T_i = T_{ctrl,i} + T_{trt,i}$$

A shrinkage factor, $\omega = \exp(\psi)$, relates observed time to counterfactual time

$$U_i = T_{ctrl,i} + \omega\, T_{trt,i}$$

How to estimate ω:

1. Choose a grid of possible values of ω
2. For grid value, ω_g, calculate U_i and calculate logrank statistics between arms
3. Best value of ω is where logrank statistic is 0 or closest to 0

Arm	Observed Time	Counterfactual Time
Treatment	T_{trt}	ωT_{trt}
Control	T_{ctrl}	T_{ctrl}
Crossover (ctrl → trt)	$T_{ctrl} + T_{trt}$	$T_{ctrl} + \omega T_{trt}$

RPSFT Adjustment

- Apply shrinkage factor, ω, to survival times of patients who switch → Calculate adjusted hazard ratio, $\widehat{\beta_A}$

- Asymptotically normal with standard error (Robins, 1992):

$$SE\left(\widehat{\beta_A}\right) = \frac{\hat{\beta}}{\sqrt{\mathrm{X}^2_{ITT}}},$$

where $\sqrt{\mathrm{X}^2_{ITT}}$ is the chi-square statistic from the log rank test that yielded ω

- Question: Is there a way to power a trial for this quantity?

RPSFT Assumptions

Informally the assumptions are:

1. There are no prognostic differences between arms at baseline
   - We're comparing counterfactual survival times. This comparison should make sense

2. The treatment effect doesn't depend on when new treatment is administered
   - Single parameter, ω, relates treatment to control. This doesn't depend on time

3. *Since ω is found with logrank test, is a proportional hazards assumption reasonable?
   - *We can use a different test statistic

Modifications to RPSFT

- Previous model for counterfactual times can be expressed more generally as

$$U_{i,\psi} = \int^{T_i} \exp(\psi * e_{it}) dt$$

"Sum" over time

Survival time

Indicator of treatment at time t

- Model above describes the mean survival time modeled by an accelerated failure time (AFT) model

- More general relationships can be explored by changing the expression inside the integral
  - Ex: Balance U_i over multiple visits, include covariates, more flexible model

RPSFT Sources

Ouwens M, Hauch O, Franzén S. A Validation Study of the Rank-Preserving Structural Failure Time Model: Confidence Intervals and Unique, Multiple, and Erroneous Solutions. Medical Decision Making. 2018;38(4):509-519

Bennett, Iain, et al. "Accounting for uncertainty in decision analytic models using rank preserving structural failure time modeling: application to parametric survival models." Value in Health 21.1 (2018): 105-109.

Sullivan, Thomas R., et al. "Adjusting for Treatment Switching in Oncology Trials: A Systematic Review and Recommendations for Reporting." Value in Health 23.3 (2020): 388-396.

Y.-K. Tu and D.C. Greenwood, Modern Methods for Epidemiology, Springer 2012, Chapter 14 https://people.maths.bris.ac.uk/~maxvd/Tilling_gEstim.pdf

Complicated original papers:

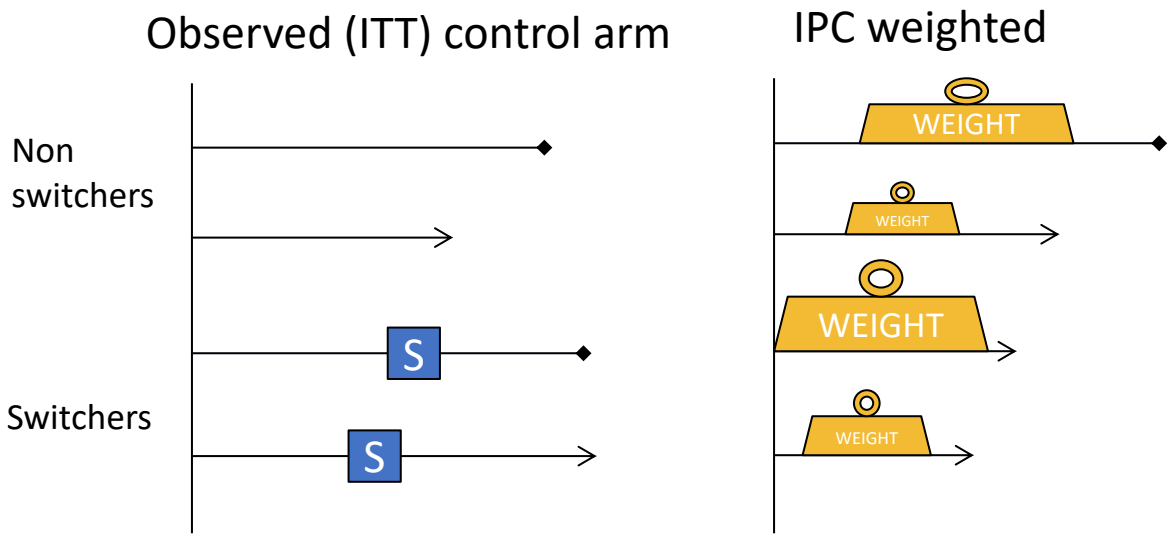
Robins, James. "A new approach to causal inference in mortality studies with a sustained exposure period—application to control of the healthy worker survivor effect." Mathematical modelling 7.9-12 (1986): 1393-1512.

Robins, James. "Estimation of the time-dependent accelerated failure time model in the presence of confounding factors." Biometrika 79.2 (1992): 321-334.

Robins, James M. "Correcting for non-compliance in randomized trials using structural nested mean models." Communications in Statistics-Theory and methods 23.8 (1994): 2379-2412.

Inverse Probability of Censoring Weights (IPCW)

- Censor patients at time of crossover and weigh likelihood
- Calculate $\Pr(\text{Switch} \mid \text{Covariates})$ using logistic regression or Cox regression
- Re-weigh the patient to mimic patient population as if no one switched (remove selection bias)
  - High weight if Pr(Switch | Covariates) close to 1
  - Low weight if Pr(Switch | Covariates) close to 0



IPCW Assumptions

The assumptions of IPCW rely on how well you can estimate $\Pr(\text{Switch})$

1. Are there unmeasured factors that influence a patients likelihood to switch and their survival time?

2. Have too many patients switched to accurately model Pr(Switch)?
   - If 95% of your patients switch, it may be difficult to say what factors influence switching
   - >80% seems to be tipping point

IPCW Sources

- Sullivan, Thomas R., et al. "Adjusting for Treatment Switching in Oncology Trials: A Systematic Review and Recommendations for Reporting." Value in Health 23.3 (2020): 388-396.

- Latimer, Nicholas R., and Keith R. Abrams. "NICE DSU Technical Support Document 16: Adjusting survival time estimates in the presence of treatment switching." (2014): 18.

More Methods

- Many methods for adjusting survival times for crossover come from causal inference
- Methods presented are special cases of structural nested failure time models (SNFTM) and g-estimation.
- Very complicated, technical literature.
- More complicated or tailored methods will probably come from these topics.

Sources

Structural nested failure time models (SNFTM)

Lok, Judith, et al. "Estimating the causal effect of a time-varying treatment on time-to-event using structural nested failure time models." *Statistica Neerlandica* 58.3 (2004): 271-295

G-estimation / G-computation

Wiley StatsRef: Statistics Reference Online, G-Computation Formula, Daniel, Rhian, https://statnav.files.wordpress.com/2017/10/g-computation-formula-preprint.pdf

Sterne, Jonathan AC, and Kate Tilling. "G-estimation of causal effects, allowing for time-varying confounding." The Stata Journal 2.2 (2002): 164-182.

Keil AP, Edwards JK, Richardson DB, Naimi AI, Cole SR. The parametric g-formula for time-to-event data: intuition and a worked example. Epidemiology. 2014;25(6):889-897.

Y.-K. Tu and D.C. Greenwood, Modern Methods for Epidemiology, Springer 2012, Chapter 14 https://people.maths.bris.ac.uk/~maxvd/Tilling_gEstim.pdf