Adjusting Survival Estimates for Treatment Switching: New Guidance and the Role of Real-World Evidence

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Speakers

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ISPOR Workshop. Overview of crossover adjustment methods

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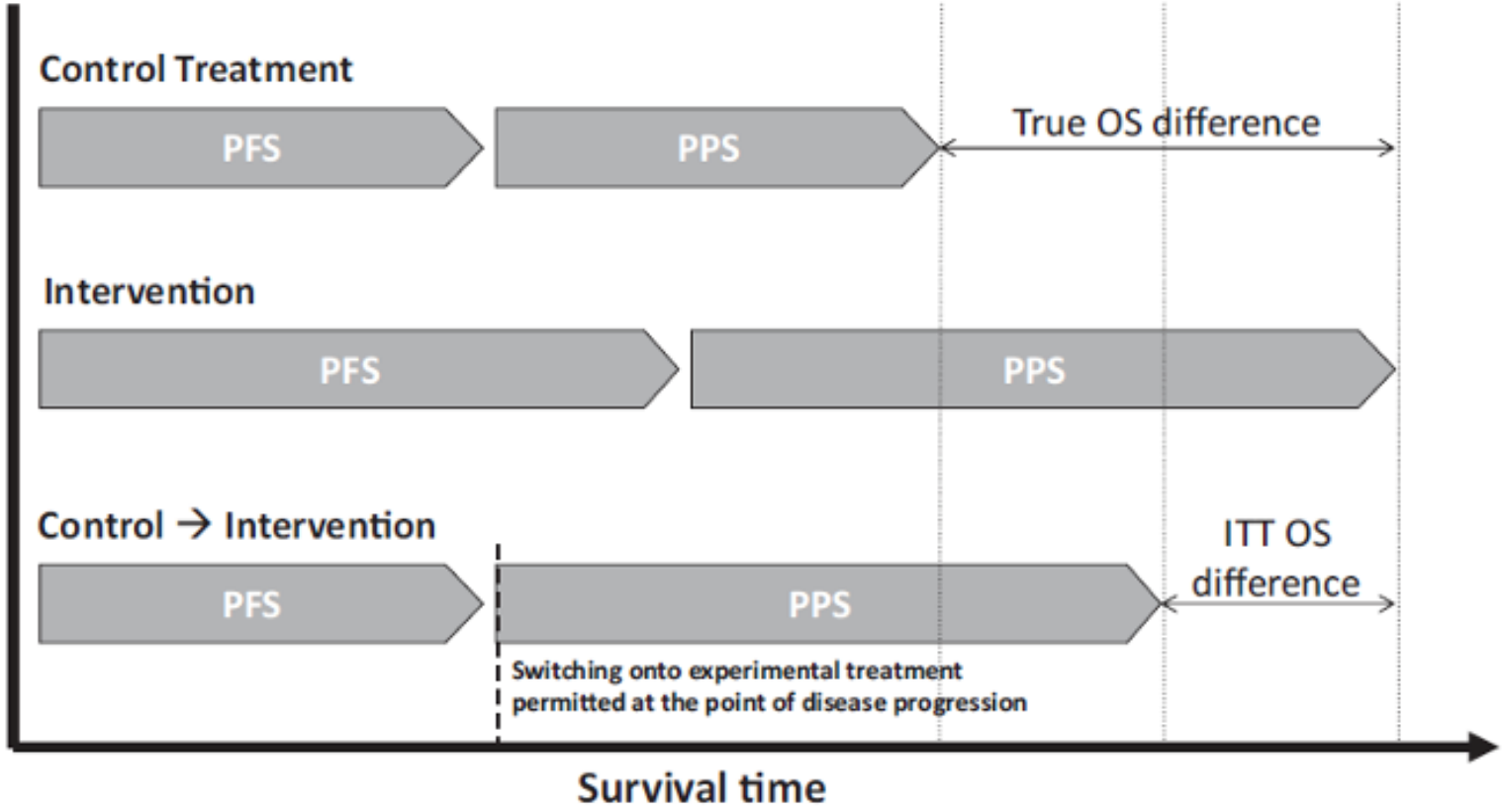
Disclosures

No conflicts of interest relevant to the content of this workshop.

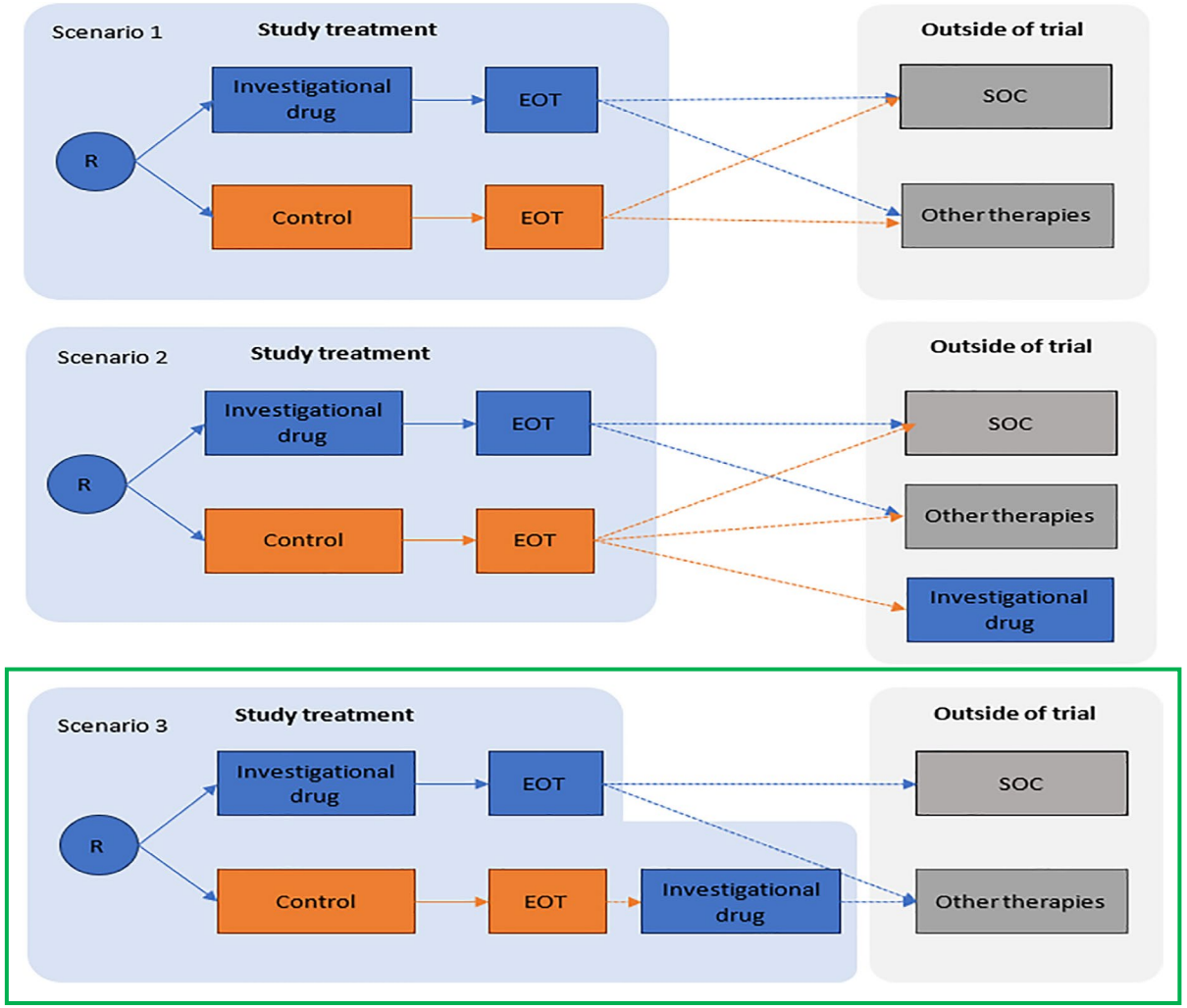
Why is crossover adjustment needed?

- Crossover or “treatment switching” causes a contamination of randomized groups
- Intention to treatment (ITT) analysis unlikely to be suitable



Sources: *Latimer NR, White IR, Tilling K, Siebert U. Improved two-stage estimation to adjust for treatment switching in randomised trials: g-estimation to address time-dependent confounding. Stat Methods Med Res. 2020;29(10):2900-2918; Abbreviations: PFS: Progression-free survival; PPS: post-progression survival; OS: overall survival; ITT: Intention to treat*

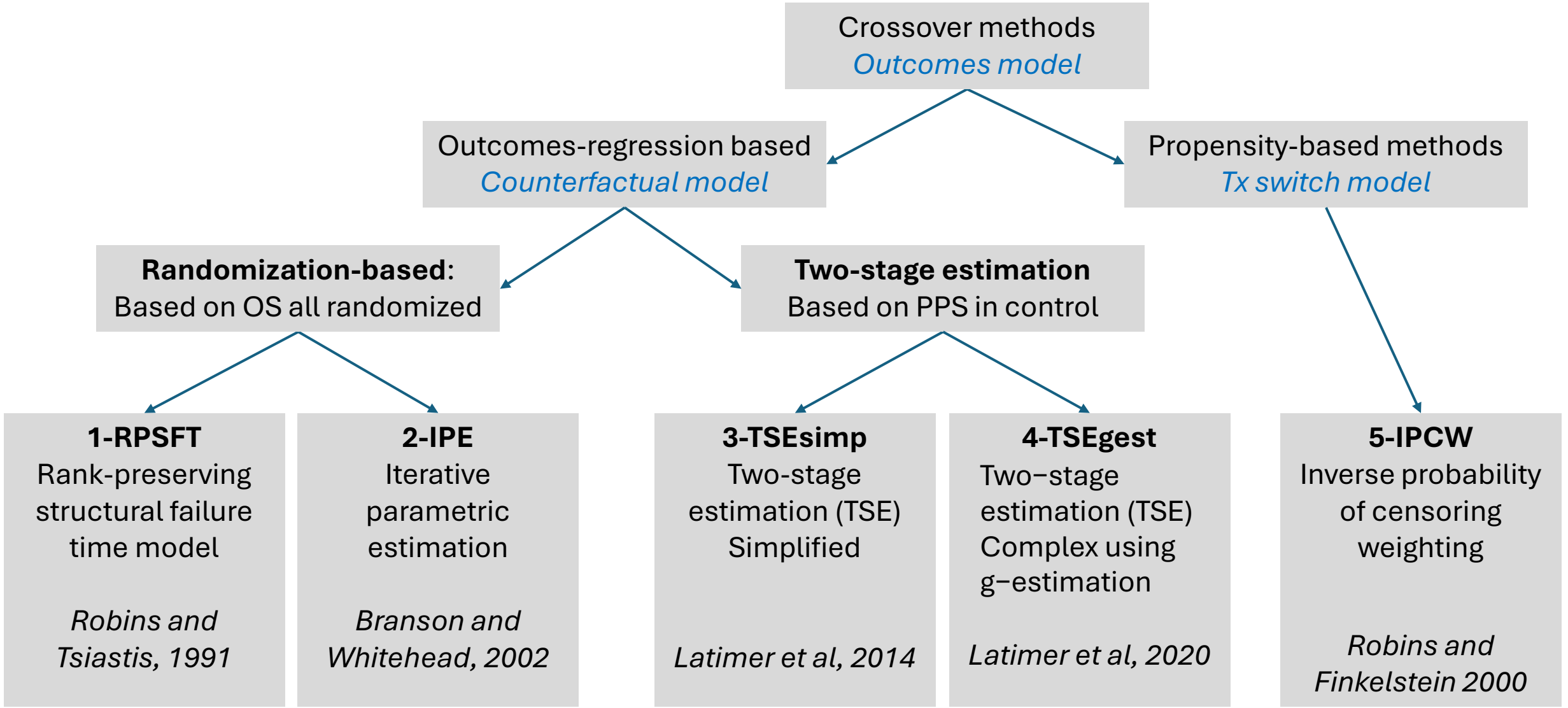
When is crossover adjustment required?



- We assume example from oncology with protocolized crossover at progression
- Crossover adjustment is required when investigational drug it is not considered a **realistic treatment pathway**
- Aim is to assess the *hypothetical* survival benefit for intervention versus control adjusted for crossover at progression assuming investigational drug not available outside of trial

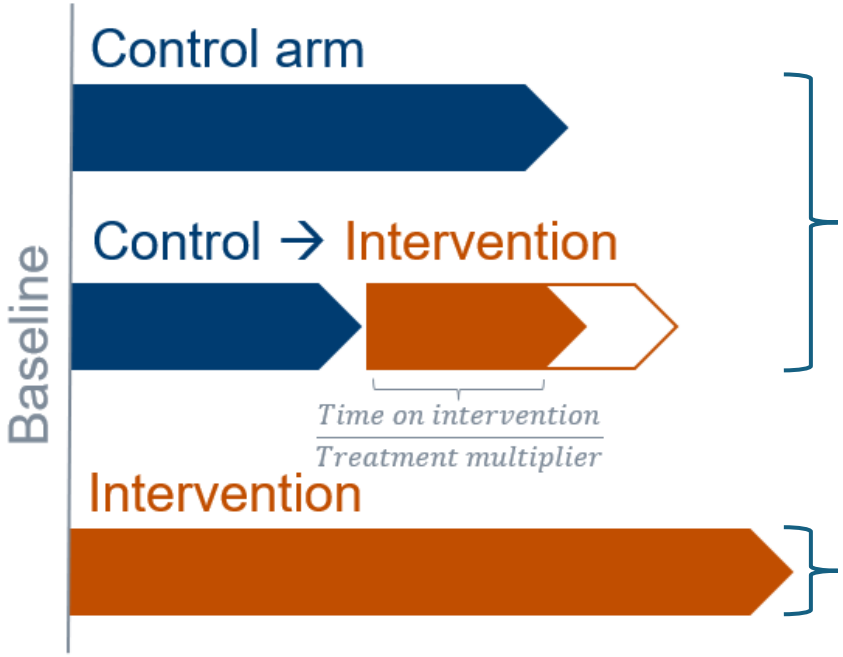
Sources: *Pharmaceutical Statistics, Volume: 21, Issue: 1, Pages: 150-162, October 2021, DOI: (10.1002/pst.2158)*

Crossover adjustment methods



Outcomes vs. propensity-based methods

Outcomes-regression based methods

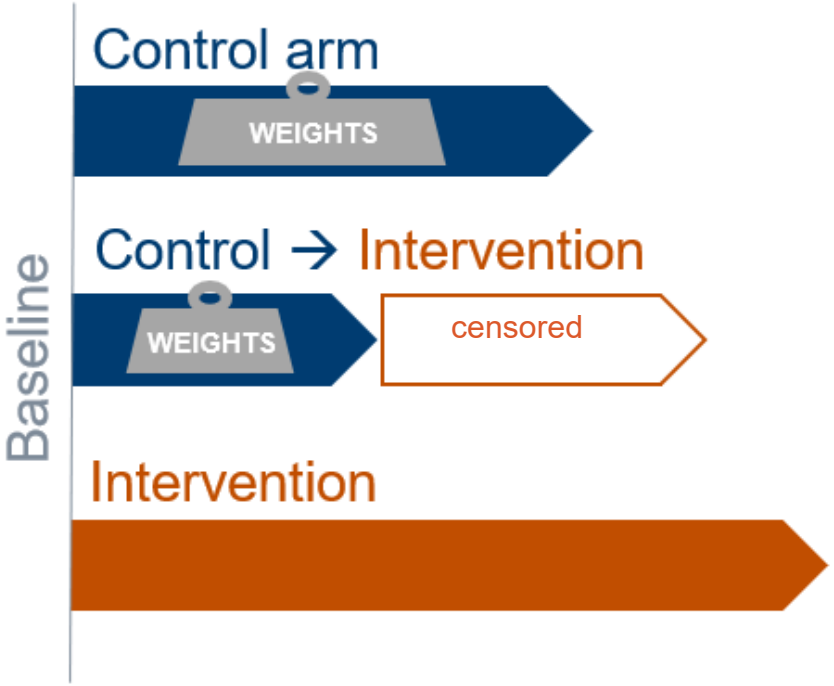


Observed control outcomes
+
Adjusted control outcomes

vs.

Intervention outcomes

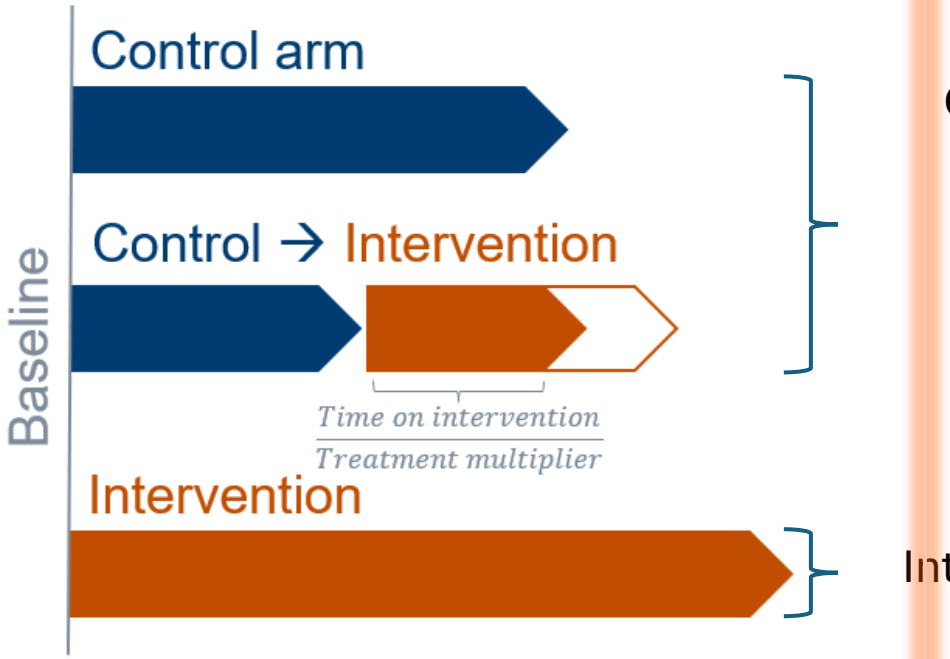
Propensity-based methods



Outcomes model:
HR Intervention vs. adjusted control outcomes
(Weighted) Cox PH model

Outcomes vs. propensity-based methods

Outcomes-regression based methods

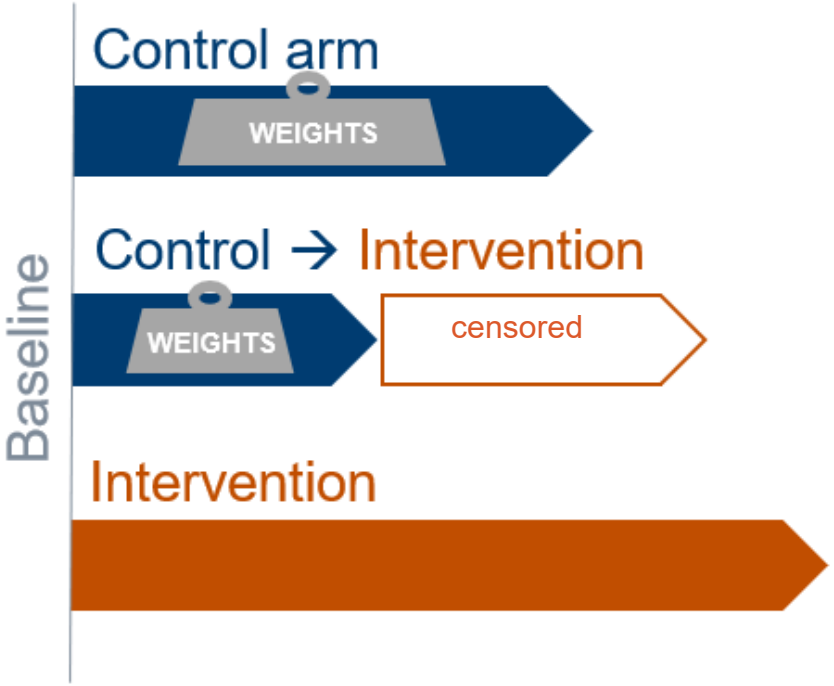


Observed control outcomes
+
Adjusted control outcomes

vs.

Intervention outcomes

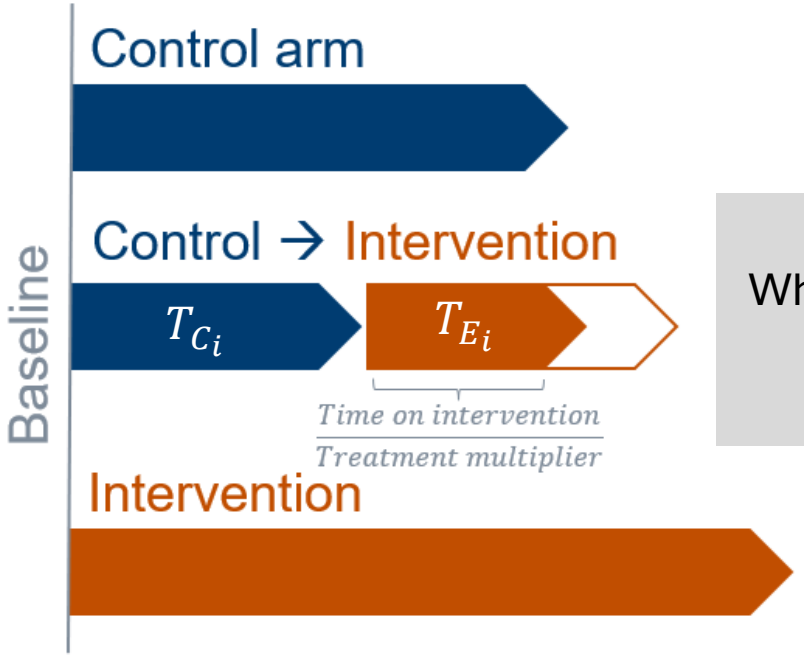
Propensity-based methods



Outcomes model:
HR Intervention vs. adjusted control outcomes
(Weighted) Cox PH model

Counterfactual model

Outcomes-regression based methods



Counterfactual model:
What would survival have been had control patients not switched to intervention?

$$U_i = T_{C_i} + (T_{E_i} \times e^{\psi})$$

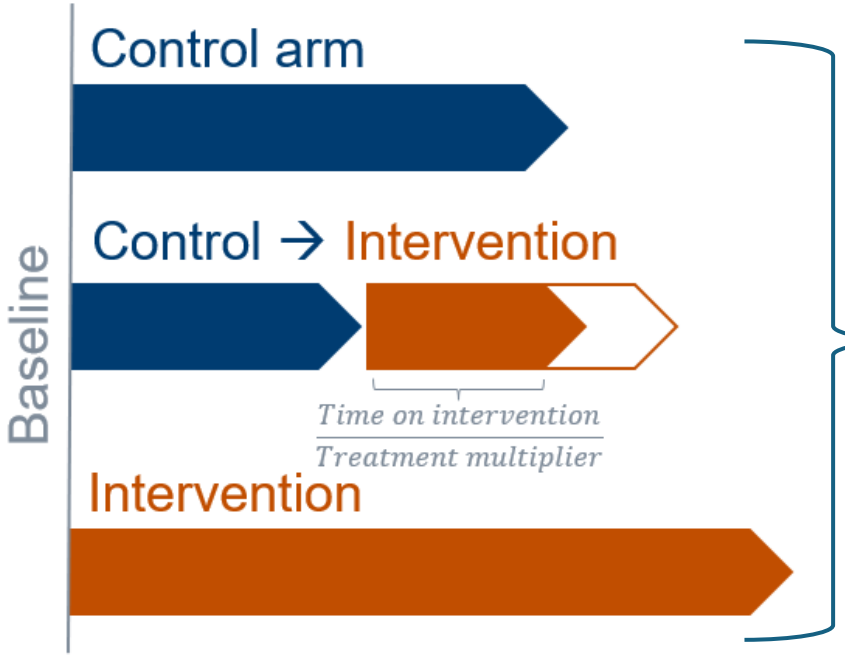
Treatment multiplicative acceleration factor (AF)
"***Shrink factor***"

Randomization-based:
Based on OS all randomized

Two-stage estimation
Based on PPS in control

Randomization-based methods: 1-RPSFT & 2-IPE

Outcomes-regression based methods



For each individual in RCT:

$$U_i = T_{C_i} + (T_{E_i} \times e^{\psi})$$

Counterfactual model

Randomization-based methods

1-RPSFT
G-estimation (non-parametric)

*No Covariates

2-IPE
Failure time model (parametric)

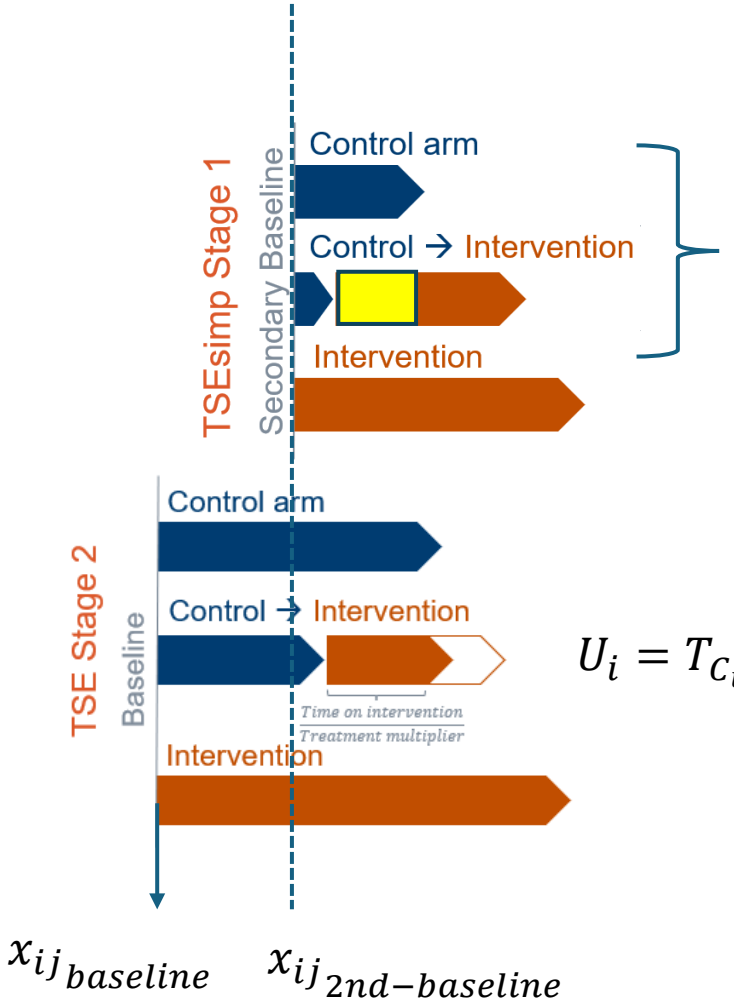
*No Covariates

Assumptions:

1. Common treatment effect
2. The only difference between randomized groups is the treatment received (i.e. independence between randomised groups and potential outcomes)
3. Parametric assumptions for IPE

Estimates value for ψ that produces the most similar untreated survival times between randomized groups

Two-stage estimation: 3-TSEsimp



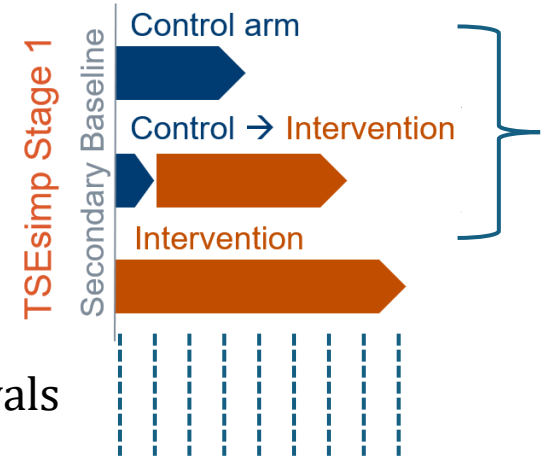
Model effect of treatment switching on PPS
(AFT)
*Adjusted for covariates at baseline & 2nd baseline

$$U_i = T_{C_i} + (T_{E_i} \times e^{\psi})$$

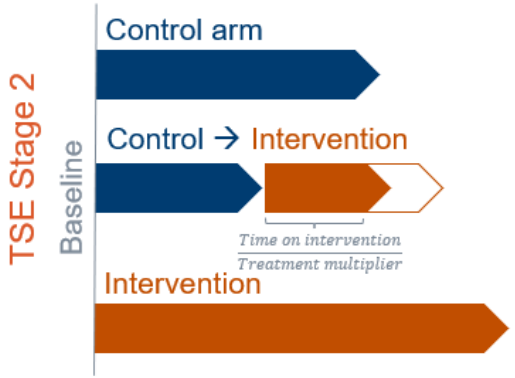
Assumptions:

1. Switching at or after a disease-related secondary baseline time-point
2. No unmeasured confounding
3. If switching happens after the secondary baseline, no time-dependent confounding between secondary baseline and time of switch

Two-stage estimation: 4-TSEgest



k intervals



G-estimation &
Treatment switch model
∗Adjusted for covariates at baseline & time-varying covariates

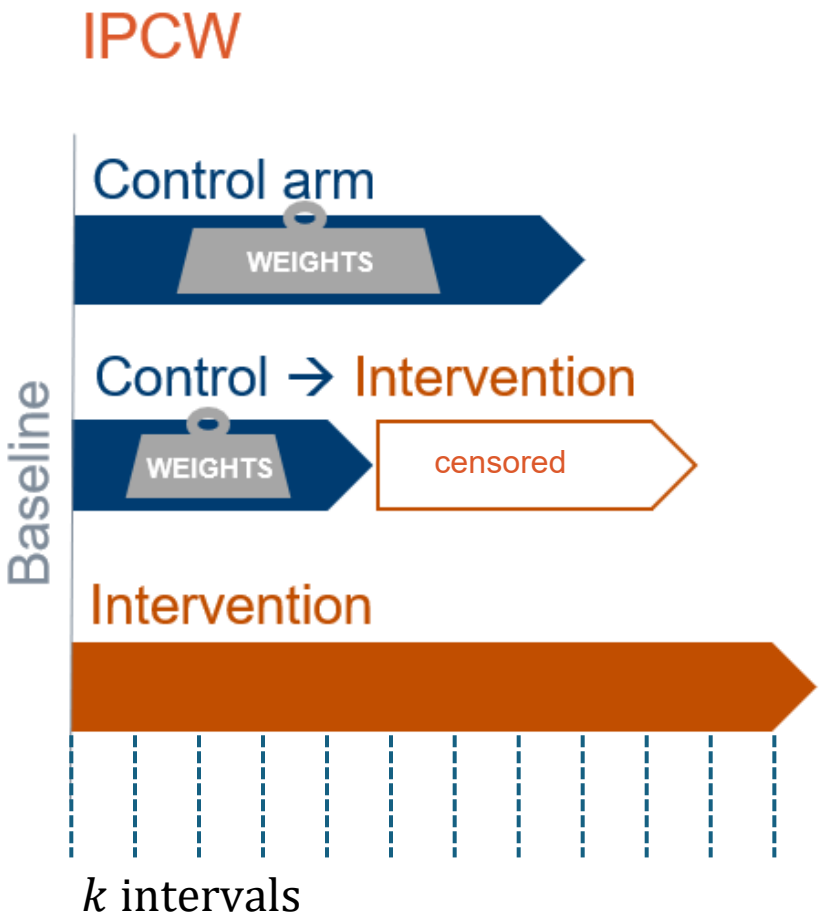
$$U_i = T_{C_i} + (T_{E_i} \times e^{\psi})$$

$$logit\big(p(E_{ik})\big) = \alpha PPS_{i,\psi} + \sum_j \beta_j \, x_{ijk}$$

Assumptions:

1. No unmeasured confounding
- If no secondary baseline, assumes independence between switch status and potential outcomes, conditional on variables measured at baseline and overtime

Propensity-based method: 5-IPCW



Tx switching model

Weights estimated using mixed effect logistic regression

∗Adjusted for baseline and time-varying covariates (k intervals)

Assumptions:

1. No unmeasured confounding

$$W(t) = \prod_{k=0}^{t} \frac{\Pr[C(k) = 0 | \bar{C}(k-1) = 0, \bar{A}(k-1), V, T > k]}{\Pr[C(k) = 0 | \bar{C}(k-1) = 0, \bar{A}(k-1), \bar{L}(k), T > k]}$$

$C(k)$: whether switching has occurred at the end of interval k,

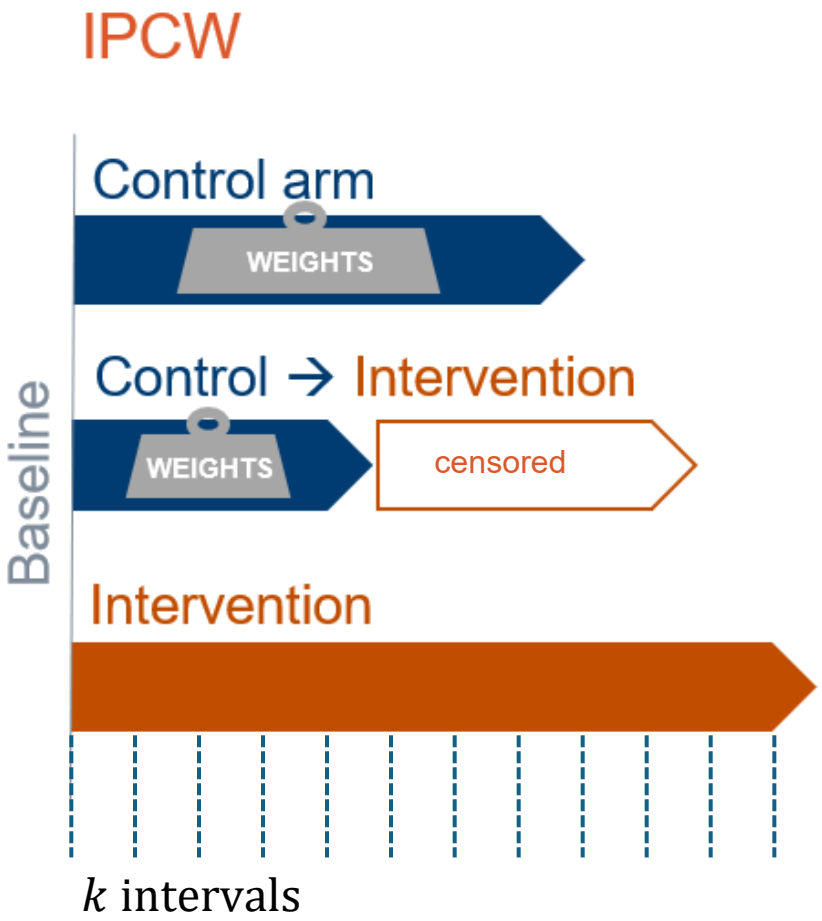
$\bar{C}(k-1)$: switching history up to end of the previous interval

$\bar{A}(k-1)$: treatment history up to end of the previous interval

V: array of baseline covariates

$\bar{L}(k)$: history of time-varying covariates including V

Propensity-based method: 5-IPCW

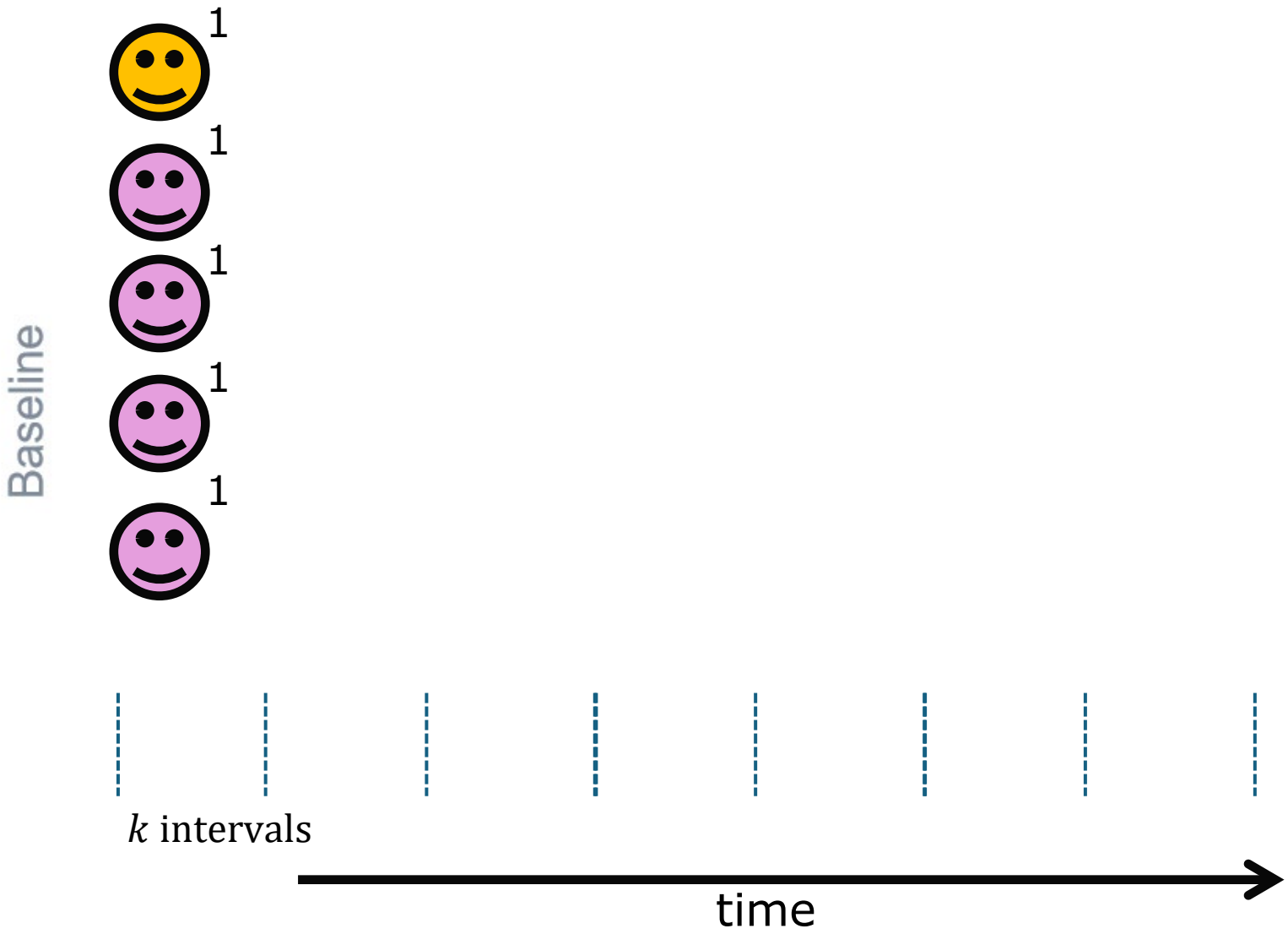


Easiest to think of this as an extension to the simple per-protocol censoring analysis.

Four steps:

1. Censor switchers at point of switch
2. Model probability of switching according to baseline and time-dependent characteristics (e.g. ECOG, HRQoL, lesion size)
3. Use probabilities to compute weights (e.g. upweight people who have similar characteristics to switchers but *didn't* switch). Weight equals the "inverse probability of not switching"
4. Use weights in a survival analysis to remove selection bias associated with censoring

Propensity-based method: 5-IPCW



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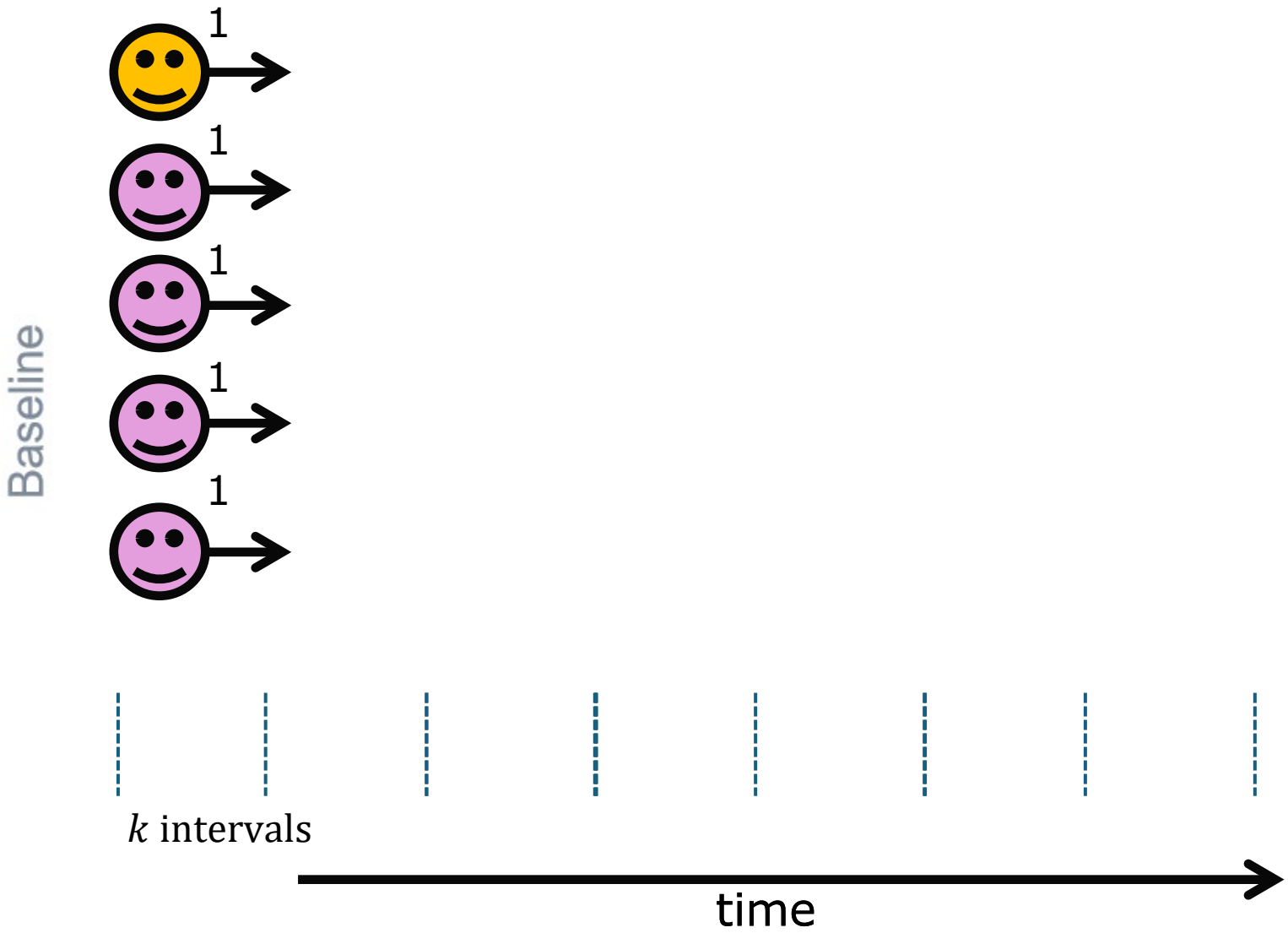
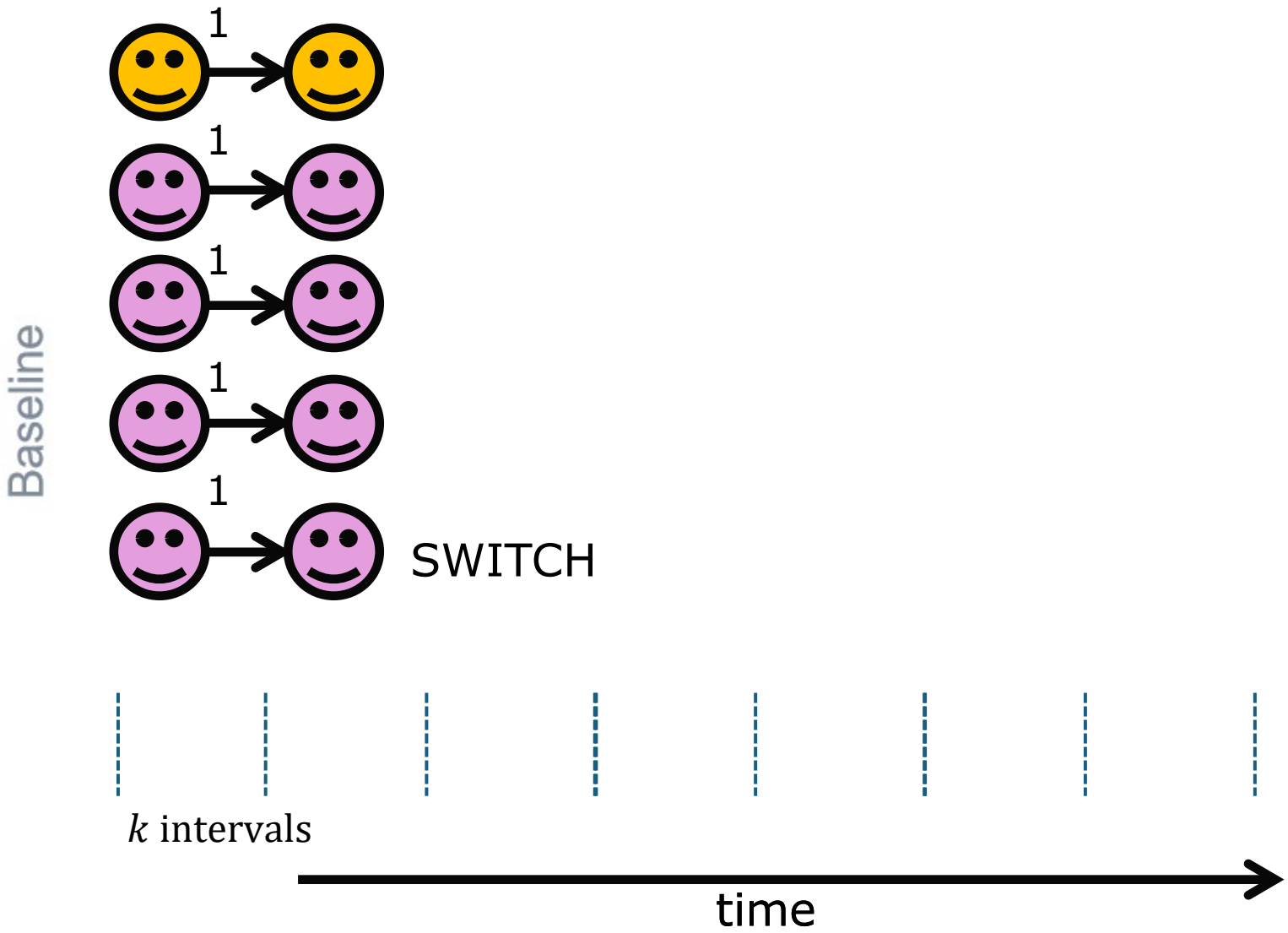
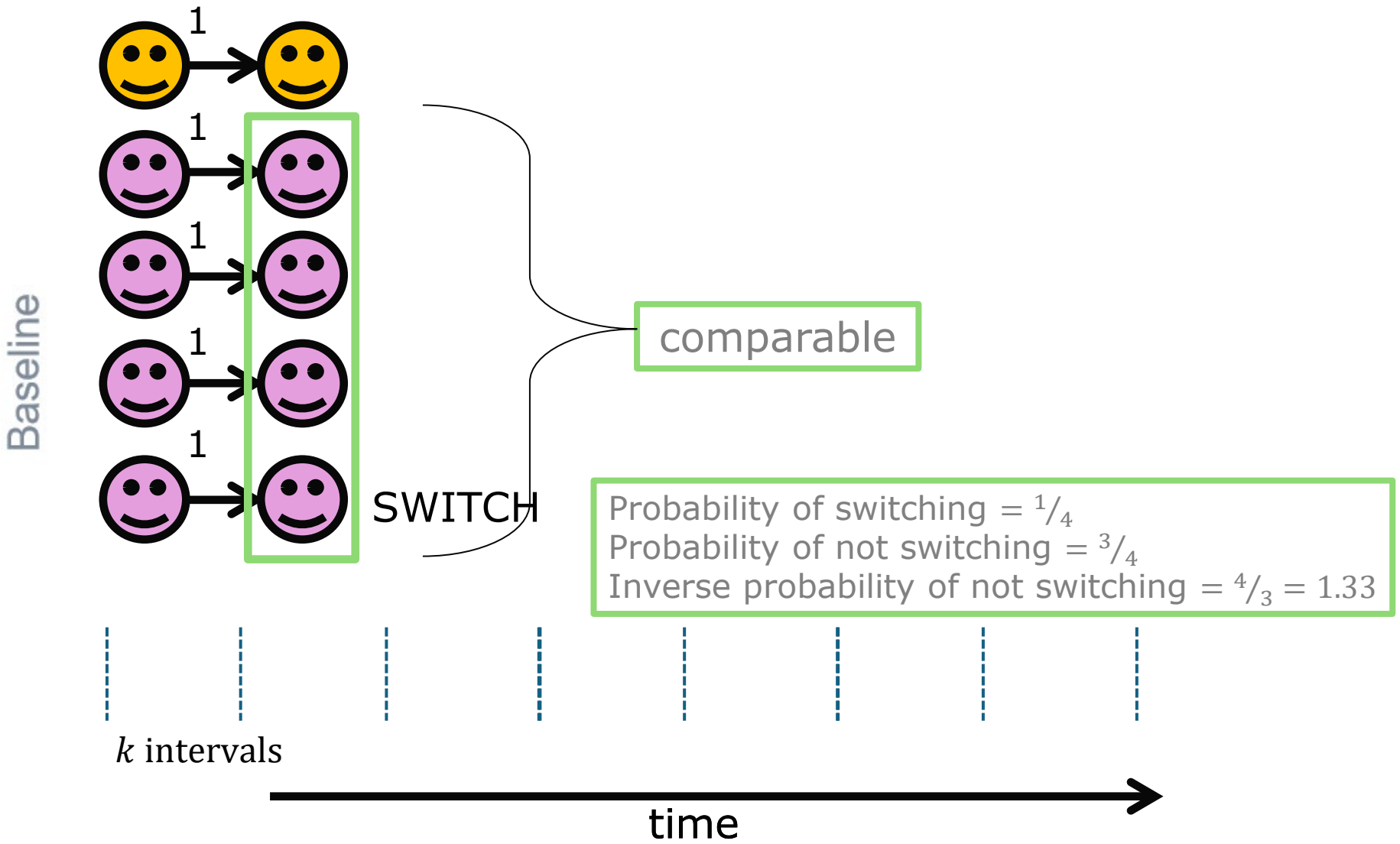


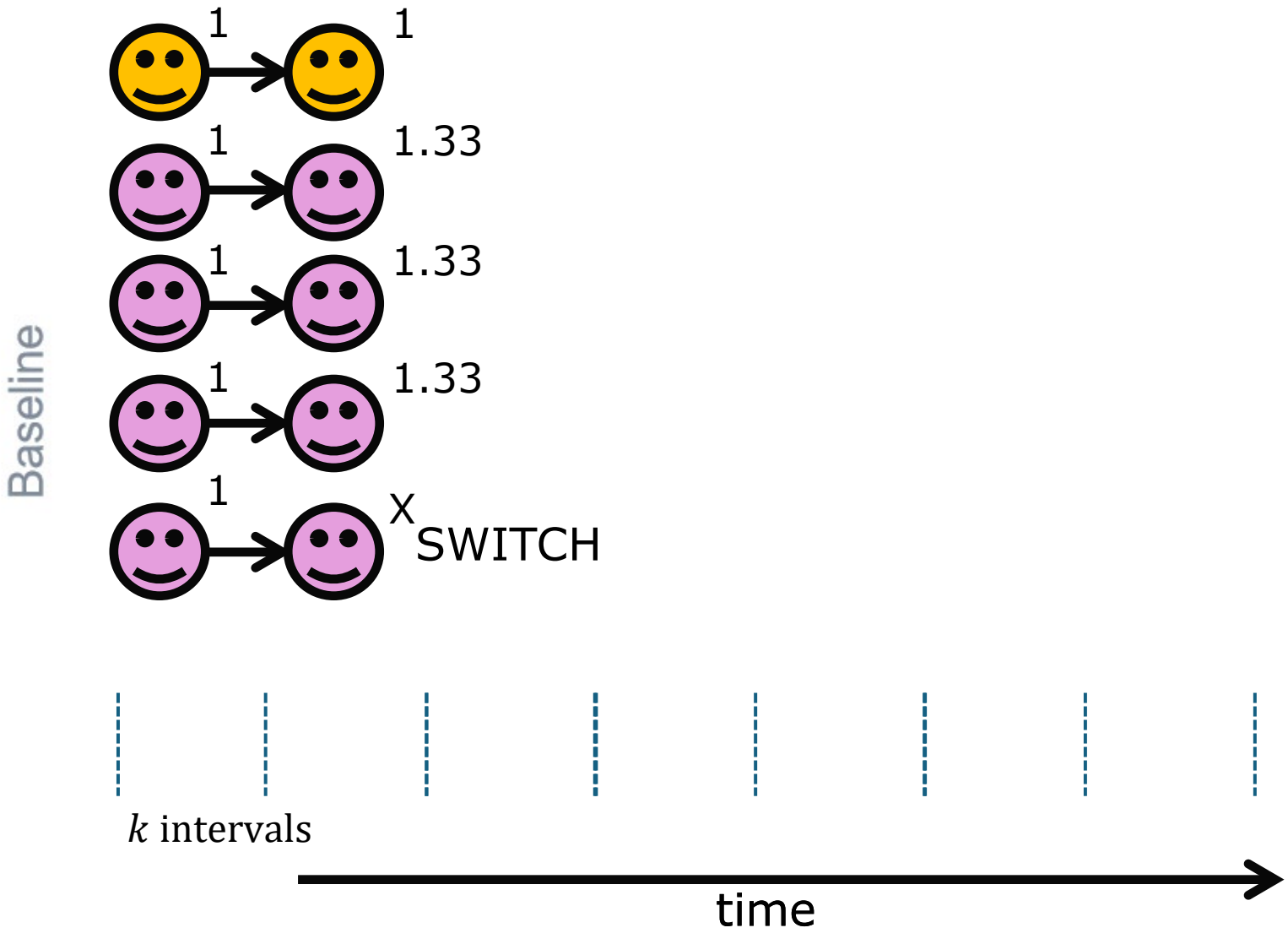
Propensity-based method: 5-IPCW



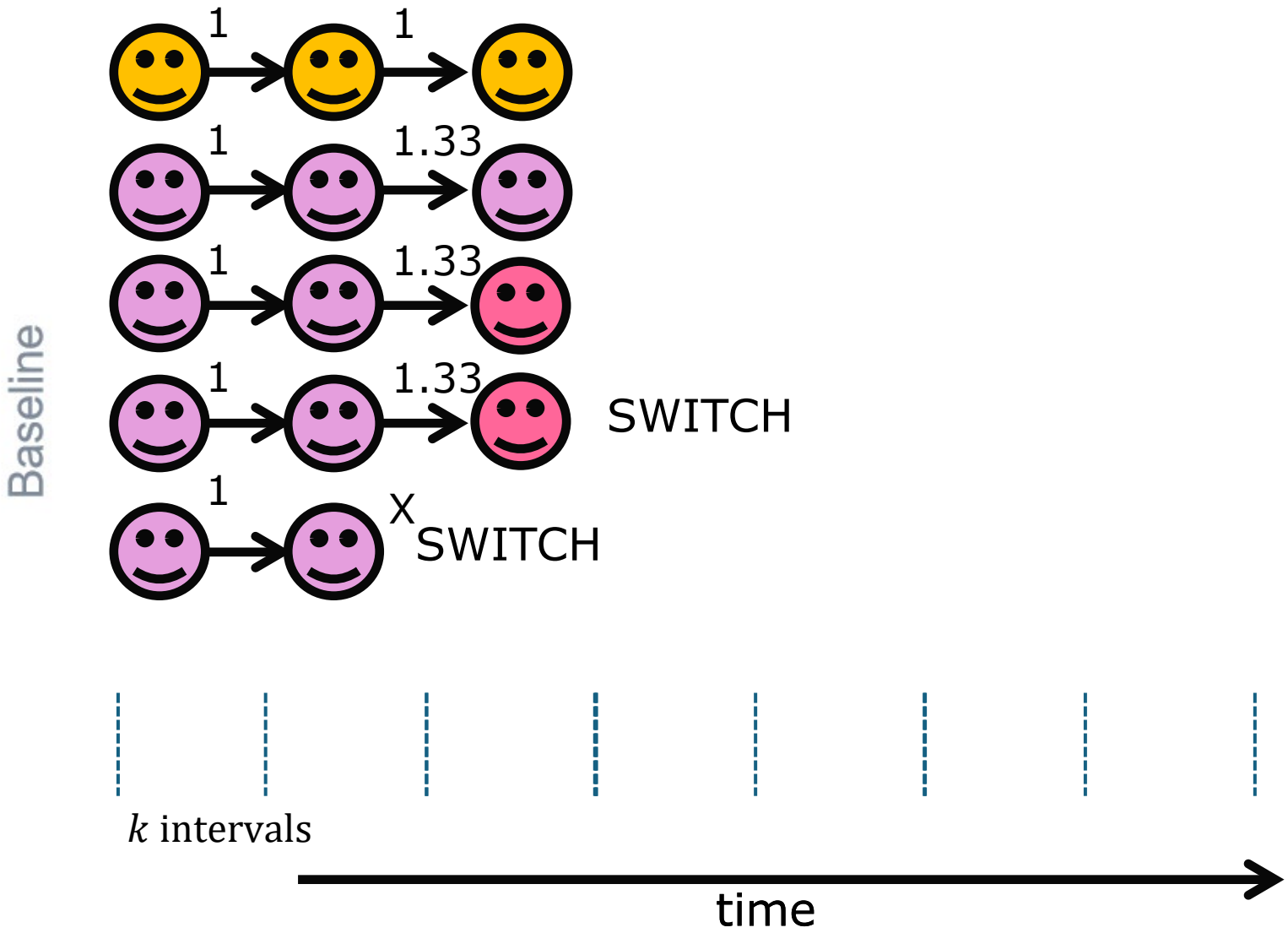
Propensity-based method: 5-IPCW



Propensity-based method: 5-IPCW



Propensity-based method: 5-IPCW



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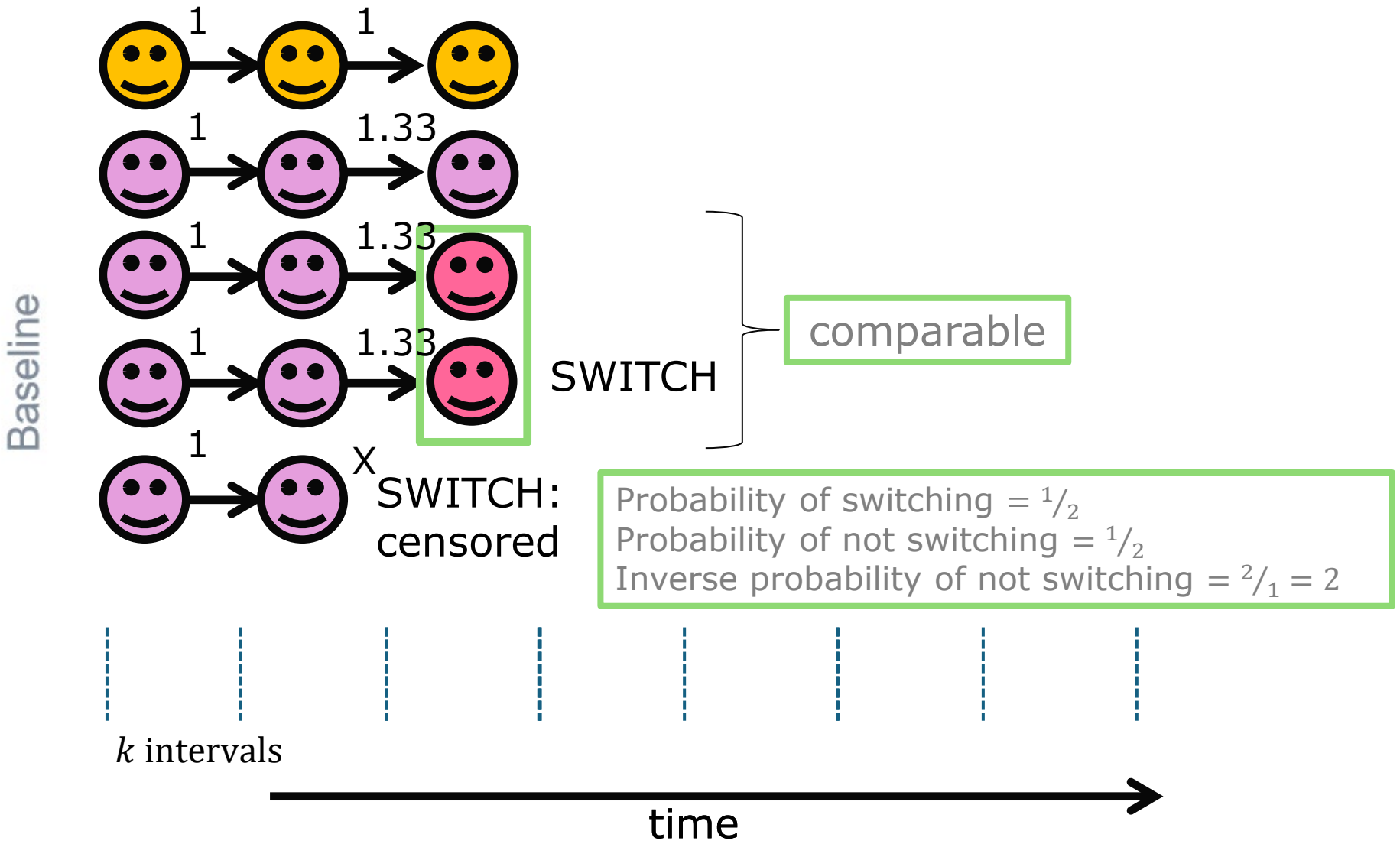

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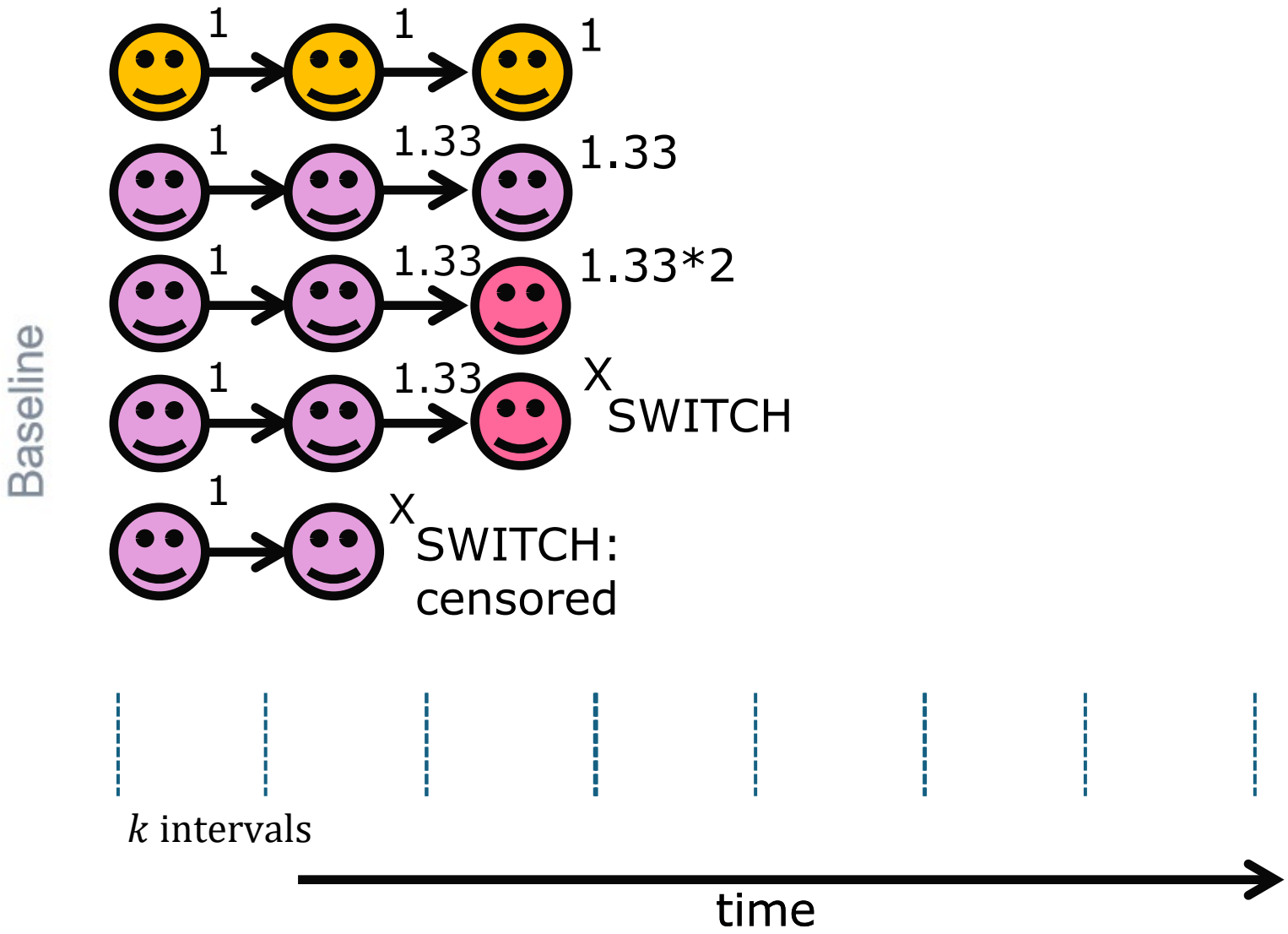

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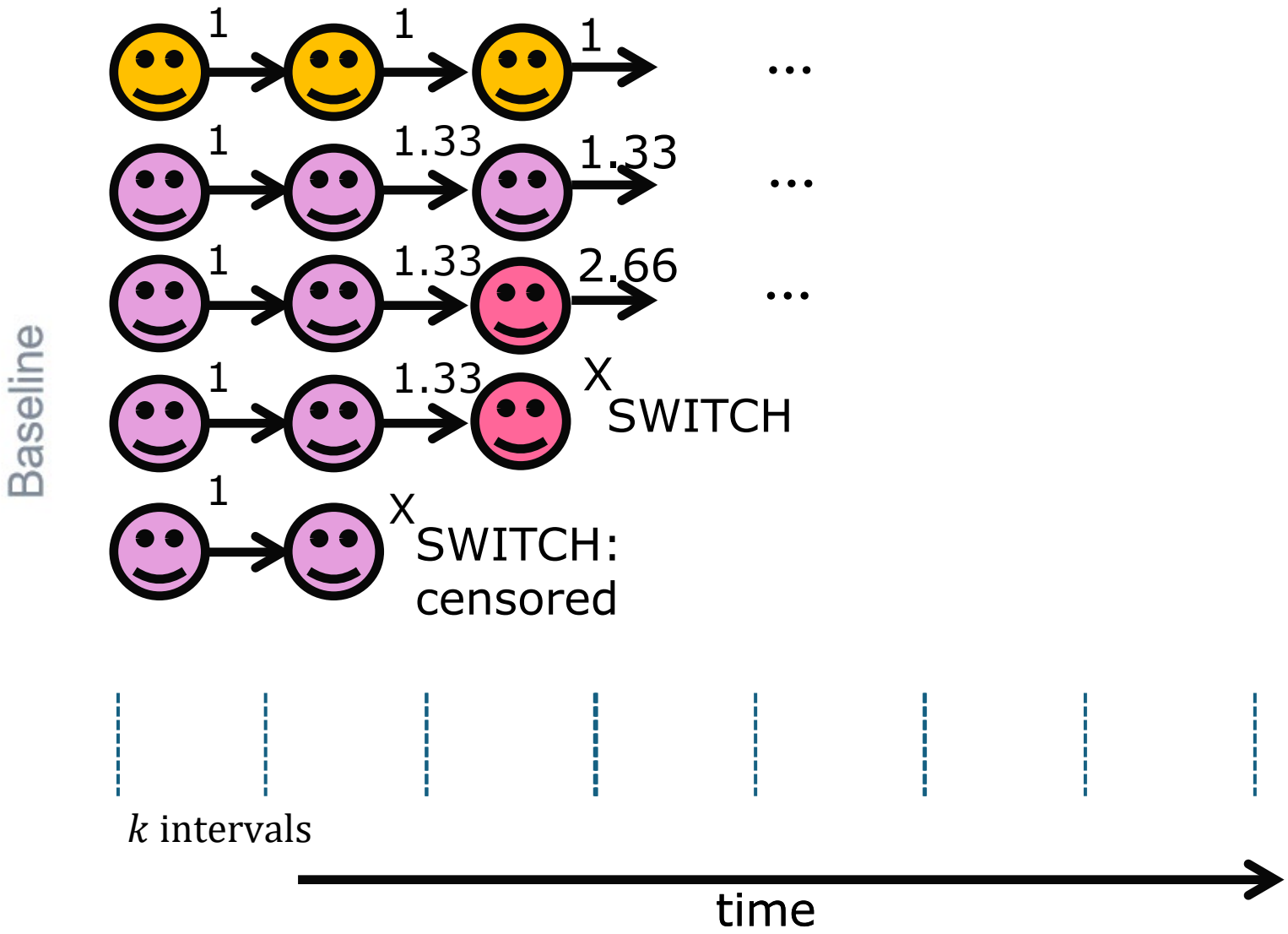
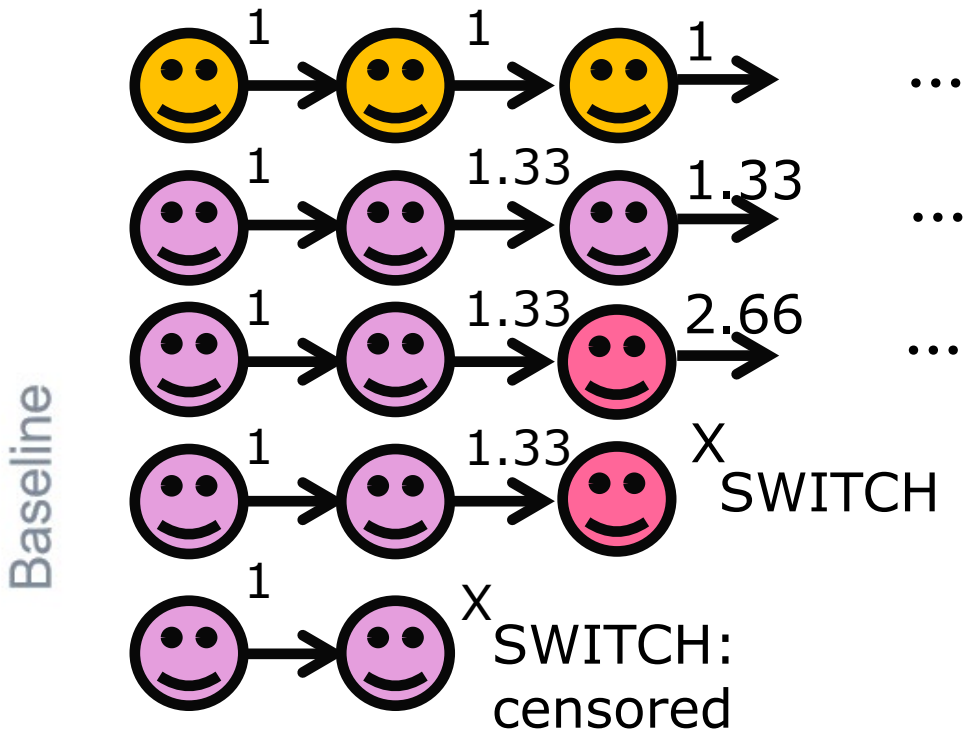


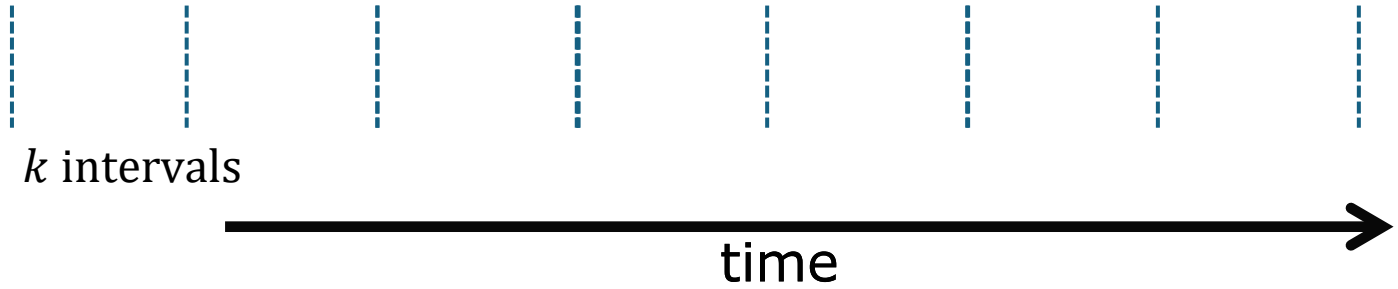
Propensity-based method: 5-IPCW



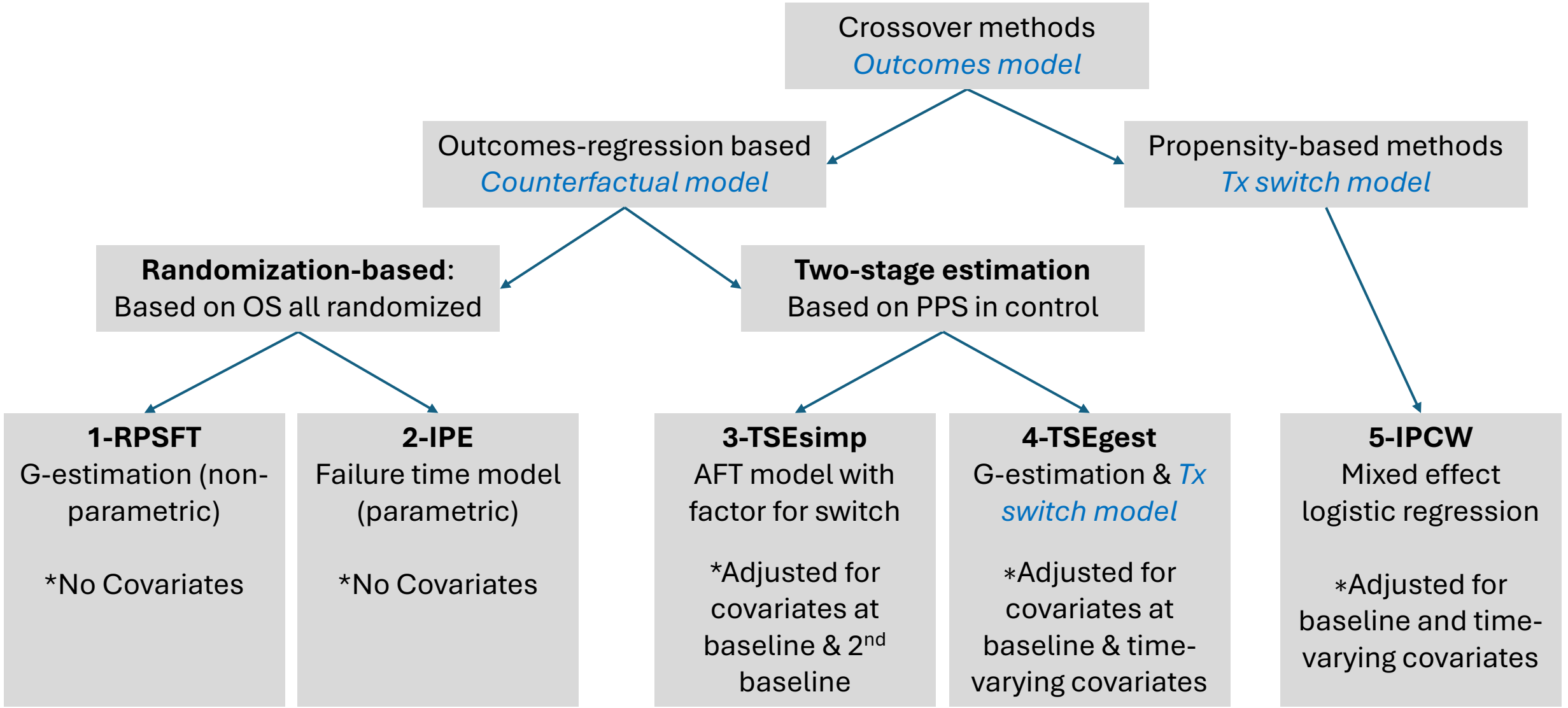
- We need to be able to distinguish which patients who have not switched are similar to those who have switched

Practical problems

- Data collection over time
- Missing data
- Model convergence
- High weights



Crossover adjustment methods



Comparing crossover adjustment methods

		Randomization-based		Two-stage estimation		Propensity-based
	Requirement	**1-RPSFT**	**2-IPE[b]**	**3-TSEsimp**	**4-TSEgest**	**5-IPCW**
Model	Model for counterfactual survival	Y	Y	Y	Y	
	Model for effect of treatment switching on PPS			Y	Y	
	Model for treatment switching				Y	Y
	Model for outcomes (Cox model)	Y	Y	Y	Y	Y
Data	Survival from full RCT including intervention arm	Y	Y			
	Date of secondary baseline			Y	Y	
	Baseline covariates that impact switch or outcome			Y	Y	Y
	Covariates (baseline or secondary baseline) that impact switch or PPS			Y	Y	
	Sufficient data on non-switchers with characteristics similar to switchers to upweight (i.e., sufficiently large N/ low crossover)					Y
	Time-varying covariates that influence switch or outcome				Y	Y
Assumption	Common treatment effect (regardless time)	Y	Y			
	Randomized groups independent from potential outcomes	Y	Y			
	No unmeasured confounding			Y	Y	Y
	Switch occurs at secondary baseline			Y	optional	
	No time-dependent confounding (secondary baseline → switch)			Y		

Notes: *Adapted from Box 1 Latimer et al. 2020.* [6] ***Abbreviations****: IPCW, inverse probability of censoring weights; IPE, iterative parameter estimation; RPSFT, rank preserving structural failure time; TSEgest, two-stage estimation involving g-estimation; TSEsimp, simplified two-stage estimation.* [b] *Requires additional assumption regarding appropriate parametric distribution as compared to RPSFT;* [*] *If secondary baseline not assumed, requires assumption of independence between switch status and potential outcomes, conditional on variables measured at baseline and over time.*

Conclusions

- Multiple methods, each relying on different set of assumptions
- Challenging to determine which assumptions are most plausible
- Availability of data covariates over time important for TSE and IPCW methods
- If high degree of crossover and/or limited sample size IPCW estimates may be biased
- When re-censoring is introduced (methods using counterfactual model) limits available follow-up, which can impact extrapolations in cost-effectiveness model

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Poll Question 1

How should you select the most appropriate crossover adjustment method?

A. Based on what methods were pre-specified

B. Based on the plausibility of assumptions from a clinical perspective

C. Based on the characteristics of the data

D. Ideally, all of the above