Adjusting Global Survival to Make Results More Relevant and Generalizable to Local Markets

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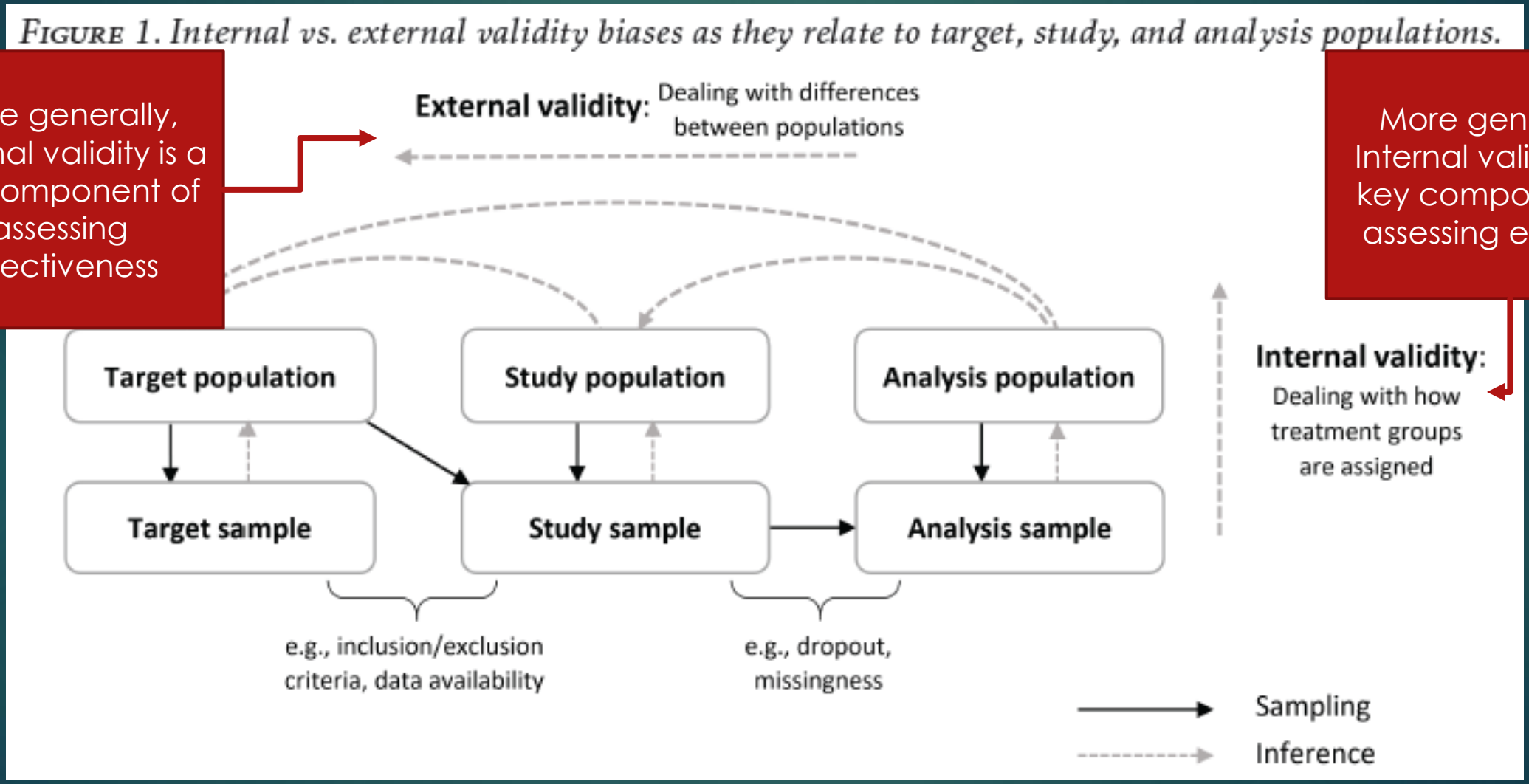
Internal vs. External Validity

More generally, external validity is a key component of assessing effectiveness

More generally, Internal validity is a key component of assessing efficacy

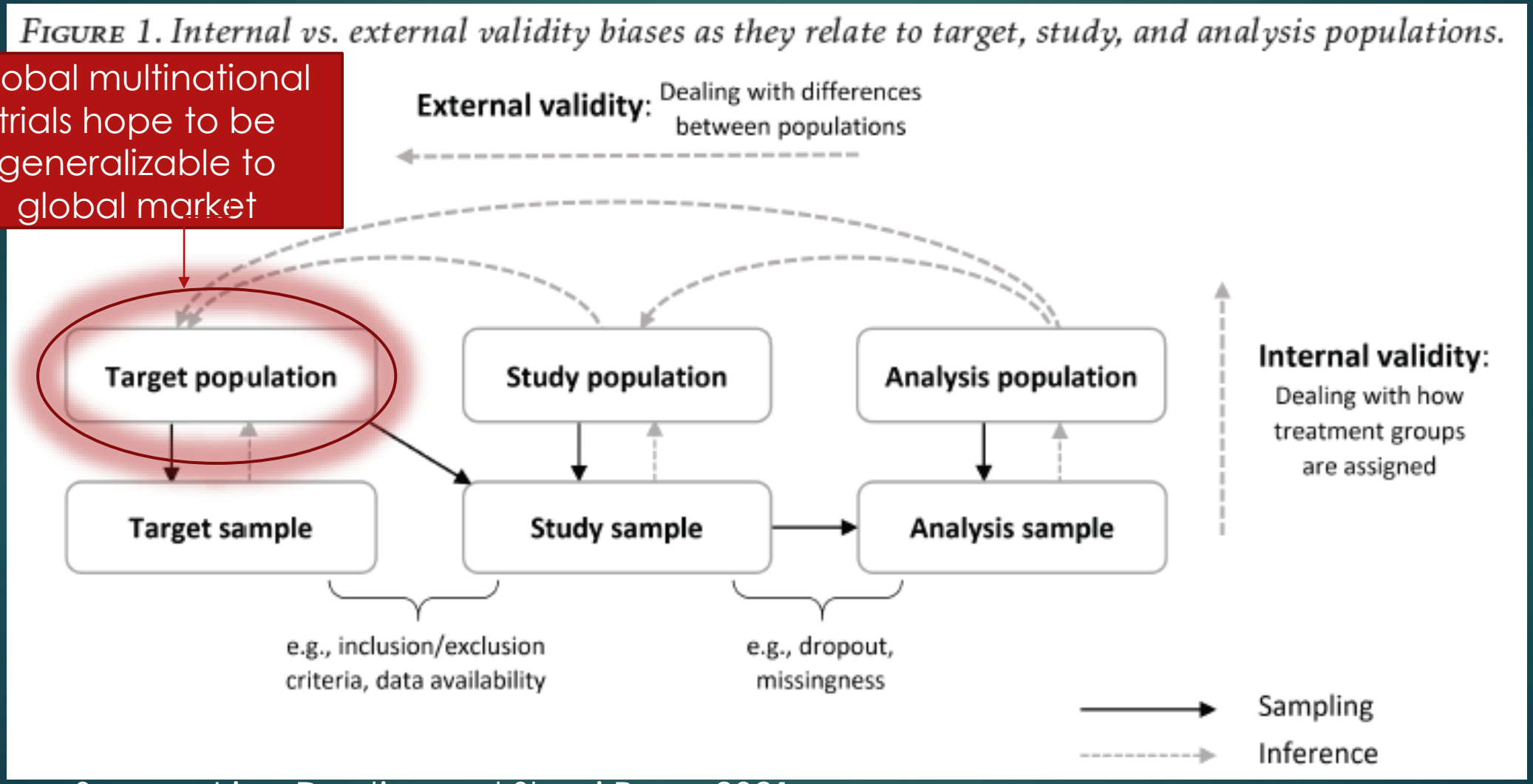
FIGURE 1. Internal vs. external validity biases as they relate to target, study, and analysis populations.



Source: Irina Degtiar and Sherri Rose. 2021.

External Validity & Generalizability

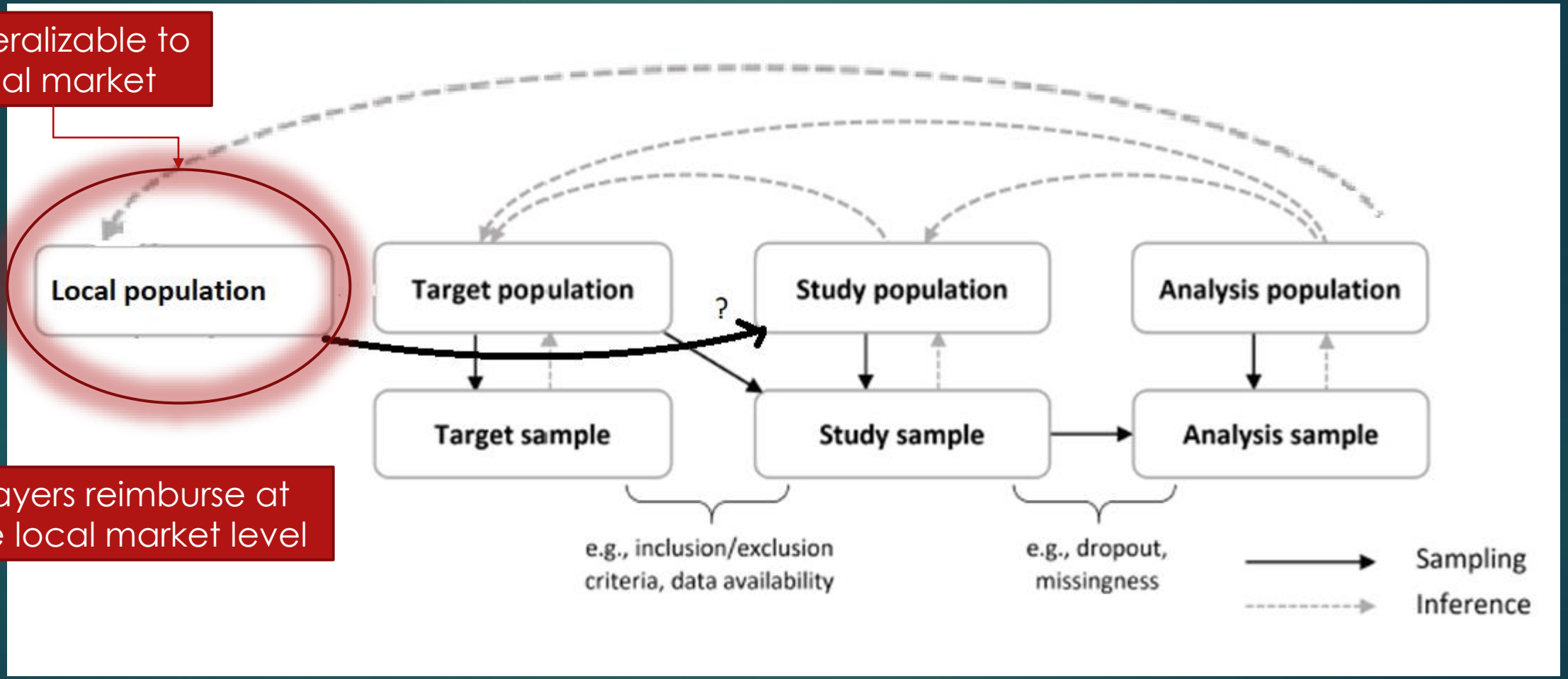
Global multinational trials hope to be generalizable to global market



Source: Irina Degtiar and Sherri Rose. 2021.

Global vs. Local Generalizability

Generalizable to local market



Payers reimburse at the local market level

What does "Bias" mean to you?

- **Statistician Perspective:** Bias means the expected value of an estimate does not equal the true value

e.g., unbiased: $E[\bar{X}] = \mu$, biased: $E[\bar{X}] \neq \mu$

- **Payer Perspective:** The efficacy estimates do not reflect the expected effectiveness
  - e.g., "clinical trials are biased and overestimate the true benefit"

Treatment switching and potential bias: An immuno-oncology example

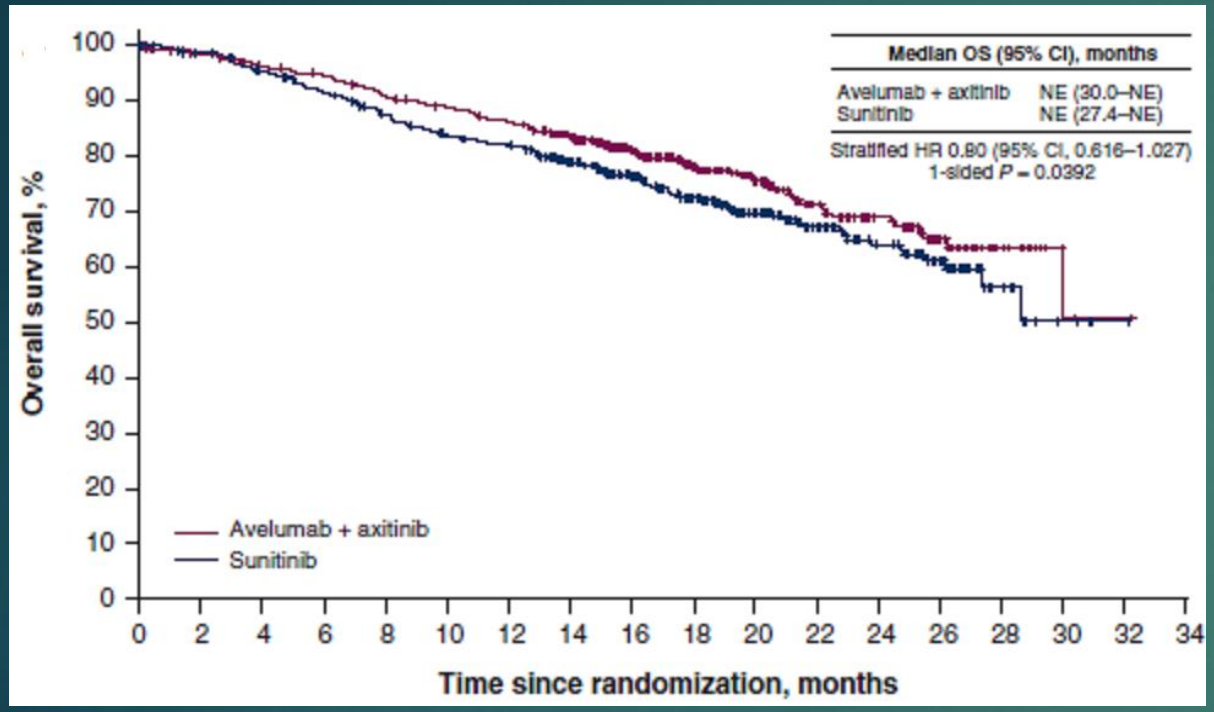
- TS

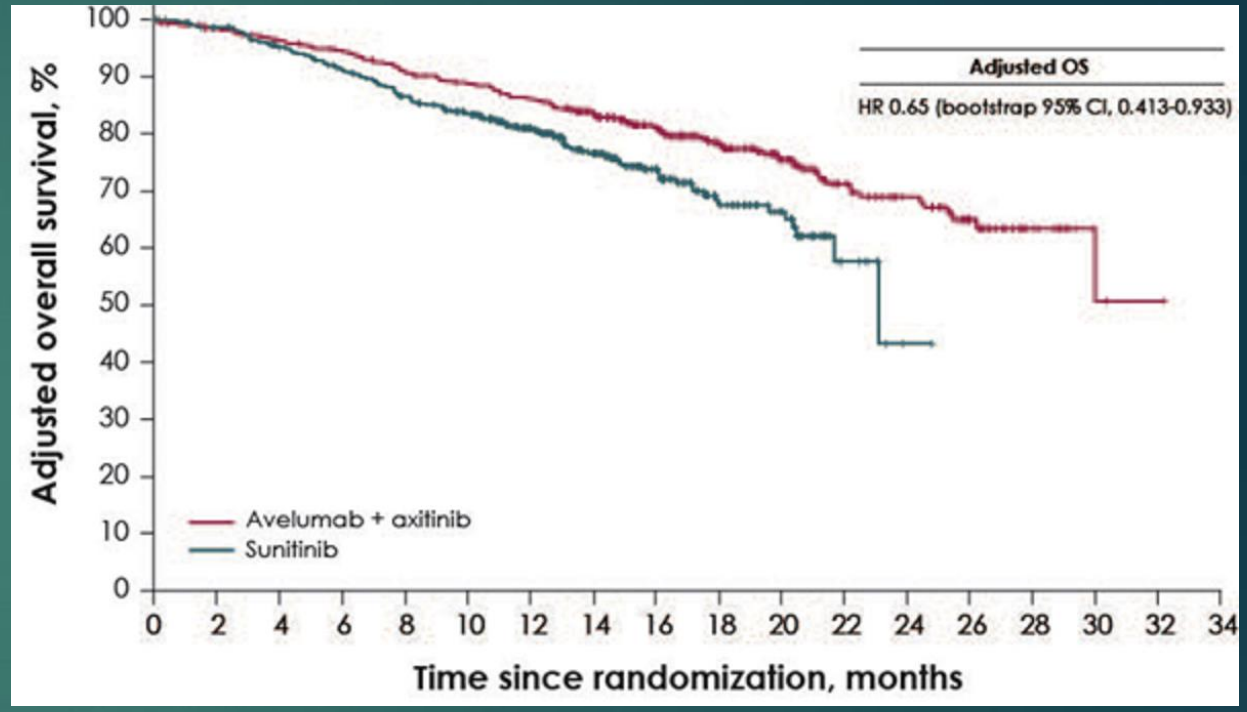
Category	Avelumab plus axitinib (*N* = 442)	Sunitinib (*N* = 444)
Patients with any follow-up anticancer treatments, *n* (%)[a]	138 (31.2)	227 (51.1)
Any VEGF or VEGFR inhibitor	118 (26.7)	123 (27.7)
Any other drug therapy	46 (10.4)	68 (15.3)
Any PD-1 or PD-L1 inhibitor	33 (7.5)	159 (35.8)

Differential use of IO (PD-1/PD-L1) treatments after progression (7.5% vs 35.8%)

Source: TK Choueiri et. al. 2020.
Similar example: N. Reinmuth et al. 2019.

Original vs. Adjusted Results





Hazard Ratio = 0.80 vs Adjusted Hazard Ratio = 0.65

Source: TK Choueiri et. al. 2020.

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Table 1. Subsequent anticancer therapy and adjusted OS in the overall population

Category	Avelumab plus axitinib (*N* = 442)	Sunitinib (*N* = 444)
Patients with any follow-up anticancer treatments, *n* (%)[a]	138 (31.2)	227 (51.1)
Any VEGF or VEGFR inhibitor	118 (26.7)	123 (27.7)
Any other drug therapy	46 (10.4)	68 (15.3)
Any PD-1 or PD-L1 inhibitor	33 (7.5)	159 (35.8)
Primary OS analysis		
Patients with event, *n* (%)	109 (24.7)	129 (29.1)
Stratified analysis		
Hazard ratio (95% CI)	0.80 (0.616–1.027)	
Adjusted OS analysis		
RPSFT analysis		
Hazard ratio (bootstrap 95% CI)	0.65 (0.413–0.933)	

Biased OS Efficacy Results

Relatively "Unbiased" OS benefit, if PD-1/PD-L1 treatment options available?

Relatively "Unbiased" OS benefit for markets without PD-1/PD-L1 treatment options?

How to account for Switching?

Common Methods for adjusting overall survival results

1. Censoring patient that switch or crossover
2. Rank Preserving Structural Failure Time models (RPSFT or RPSFTM)
3. Inverse Probability of Censoring Weighting (IPCW)
4. Two-stage estimation (TSE) methods

Source: Latimer NR, Abrams KR. 2016.

Censoring

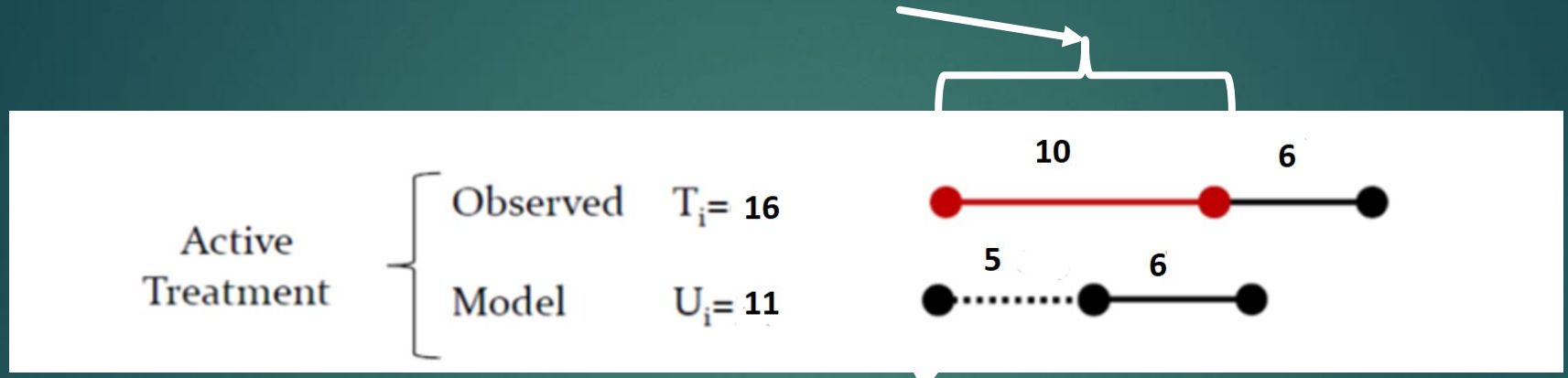
- Option 1: Exclude patients who switched to subsequent therapy
- Option 2: Censor patients' data starting from the time of switch

Key PROs & CONs :

- Easy for payers to understand
- Payers may view it is as a relatively "objective analysis"
- Does not require "pre-planned additional data collection"
- Very susceptible to selection bias, which may draw payer criticism

Rank Preserving Structural Failure time (RPSFT)

On-treatment period for experimental arm



Estimate % increase in time (use as a correction factor)

This correctin factor (ψ_0) is used to discount the time after switching to "similar" treatment

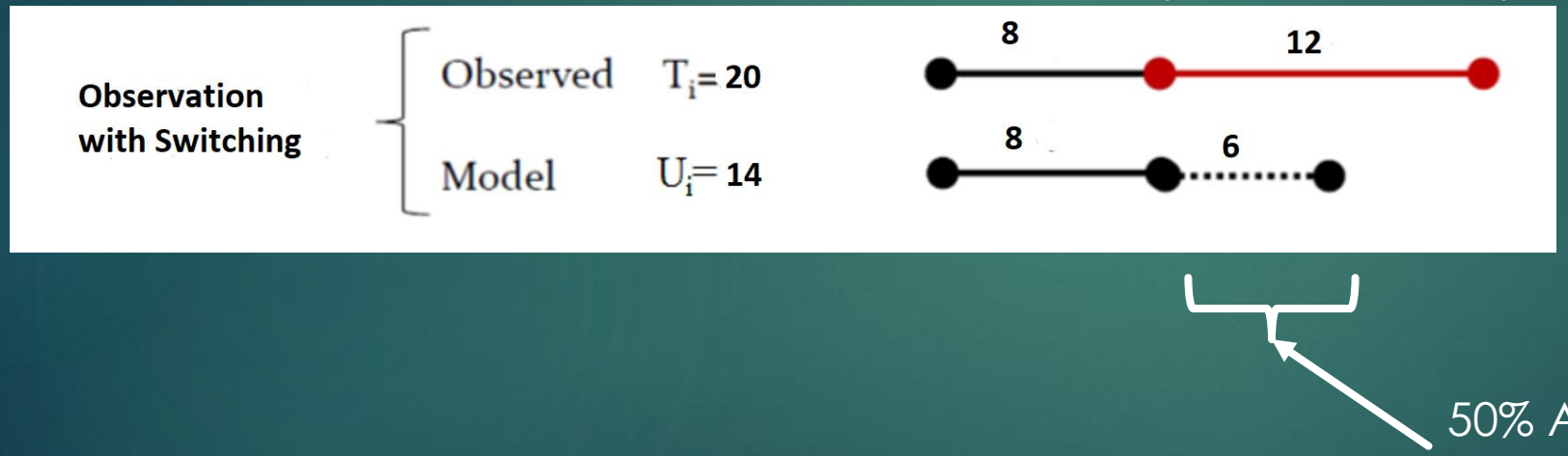
Note: If $exp(\psi_0) = 0.5$, a 50% increase in time while on treatment

Methodologic Reference:, Ishak KJ et al. 2014

Illustrative examples: Robins JM, Tsiatis AA. 1991., Korhonen P, et al. 2012.

RPSFT Models Adjustment via Acceleration Factor

Period after crossover or treatment switching



Original survival time for Example patient is 20 months

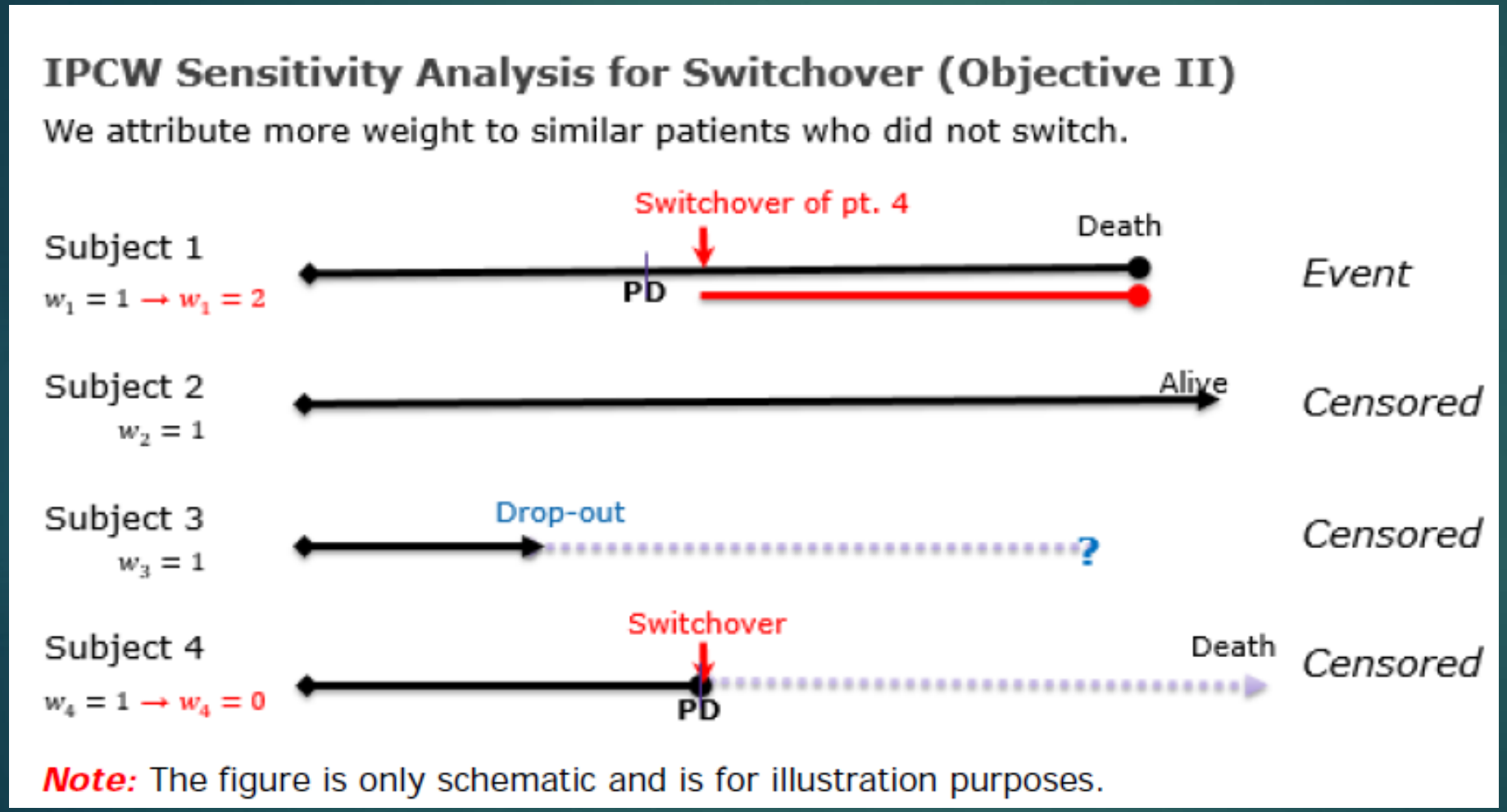
50% Adjustment is applied to period after treatment switching

Key PROs & CONs for RPSFT

- Complex and difficult to explain to payers
- Viewed as relatively "objective analysis" by payers and regulators
- Typically requires class effect assumption which payers may reject
- Does not require "pre-planned additional data collection"
- Cannot handle more complex switching scenarios

Illustrative examples: Robins JM, Tsiatis AA. 1991., Korhonen P, et al. 2012.

Inverse Probability of Censoring Weighting (IPCW)



Approach assumes no unmeasured confounders.

Approach may be viewed as more subjective then censoring or RPSFT

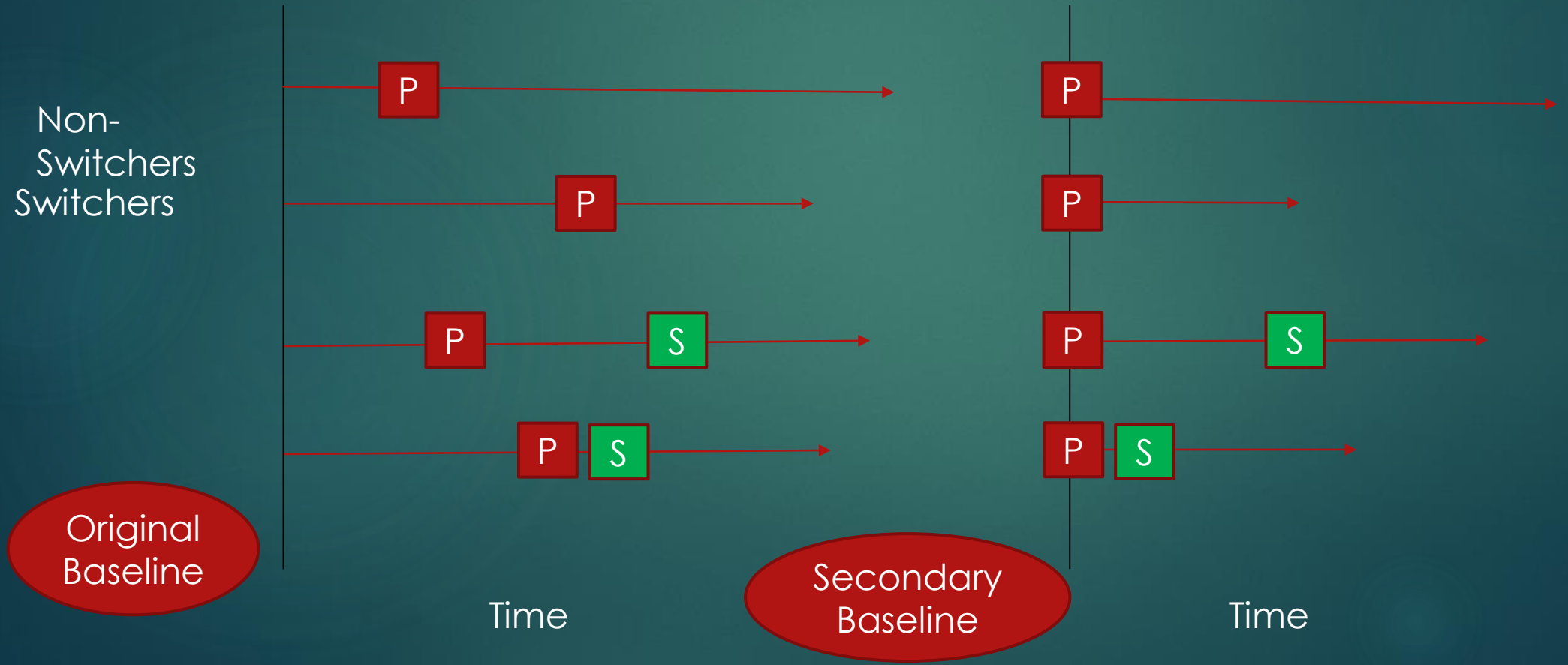
Methodologic Reference: Robins JM, Finkelstein DM. 2000.

Key PROs & CONs for IPCW

- Relatively complex and may be difficul to explain to payers
- Assumes no unmeasured confounders which payers may reject
- May be viewed as a “subjective analysis” by payers
- Require extensive data collection after progression
- Likely requires “pre-planned additional data collection”
- Cannot handle more complex switching scenarios

Two-stage estimation method (TSE)

- First stage
  - Identify a secondary baseline
  - Analyze period after secondary baseline as an "observational study"
  - Use regression analysis (e.g. a failure time model) to estimate the benefit of switching



Two-stage estimation method (TSE)

- Second Stage
  - Similar to RPSFT, use the estimate benefit, i.e. " to adjust the survival times after switch
  - Unlike RPSFT, time from original baseline to progression has no influence on the adjustment

The correction factor used to adjust time after switch is a function of baseline and post-baseline covariates.

Methodological and applied references: Latimer NR et al. 2017, Skaltsa K et al. 2017

Key PROs & CONs for TSE

- Complex and difficult to explain to payers
- Assumes no unmeasured confounders which payers may not accept
- May be viewed as a more "subjective analysis" by payers
- Requires extensive data collection after progression
- Likely requires "pre-planned additional data collection"
- Has the potential to handle more complex switching scenarios

Conclusions

- If the observed switching is likely to occur in a local market, naïve analysis of trial data may be generalizable enough for payers
- If the observed switching is not likely to occur in a local market, statistical adjustments can make the results more generalizable for payers.
- A range of techniques exist, but selection of the optimal approach is dependent on covariate availability, audience for results, and tolerance for specific assumptions.

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