How about those estimands for my cross-over study?

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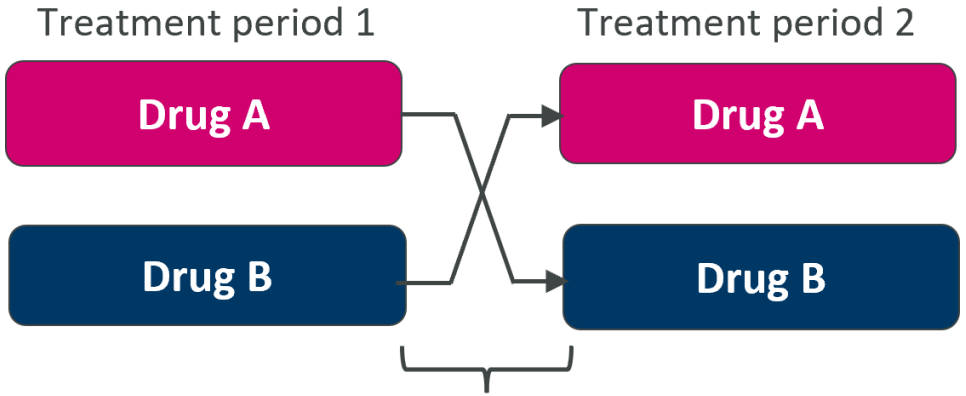
What is a cross-over study?

- Subjects receive multiple treatments in sequence. Efficient due to within-subject comparisons.
- Setting: Stable condition, feasible length of treatment periods, non-curable treatment.
- Common in clinical pharmacology studies but are also used in efficacy settings.



Why cross-over trials need estimand-specific thinking

- Standard cross-over analyses may not target the estimand of interest.
- Cross-over trials can require tailored methods to align the analysis with the intended estimand.
  - Intercurrent event (ICE) in period j can remove or alter information for period $j + 1$
  - Analysis model not just a technical choice, impacts whether the estimate matches the intended estimand.
- We will show illustrative examples and propose approaches to target estimation under key ICE strategies.
  - Efficacy trial: while-on-treatment, composite, treatment policy
  - Clinical pharmacology trials: while-on-treatment, principal stratum

How do I model my data?

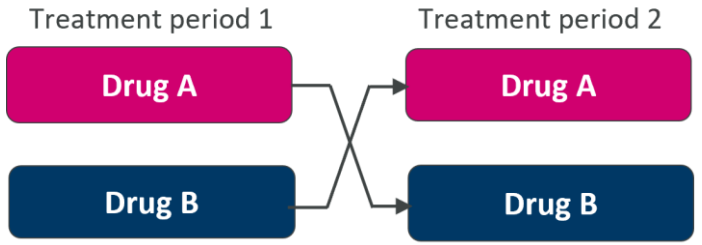
period sequence error

$$Y_{ijk} = \mu + p_j + t_{l(i,j)} + \cancel{s_i} + b_{ik} + e_{ijk}$$

intercept treatment subject

$e_{ijk} \sim N(0, \sigma^2)$

$b_{ik} \sim N(0, \sigma_S^2)$ or fixed



SUBJECT	SEQUENCE	PERIOD	TREAT	Y	YNUM	YNUM
1	AB	1	A	2.00	y111	y11
1	AB	2	B	1.25	y121	y12
2	BA	1	B	19.25	Y211	y21
2	BA	2	A	21.25	y221	y22
3	AB	1	A	30.00	y112	y31
4	BA	1	B	6.50	y212	y41

Estimation under random subject model

Effect comparing treatments B vs A: weighted average

SUBJECT	SEQUENCE	PERIOD	TREAT	Y	YNUM
1	AB	1	A	2.00	y11
1	AB	2	B	1.25	y12
2	BA	1	B	19.25	y21
2	BA	2	A	21.25	y22
3	AB	1	A	30.00	y31
4	BA	1	B	6.50	y41

$$\hat{\beta} = \underbrace{\left(\frac{2\sigma_s^2 + 2\sigma^2}{2\sigma_s^2 + 3\sigma^2}\right)}_{w_1} \frac{y_{12} - y_{11} + y_{21} - y_{22}}{2} + \underbrace{\left(\frac{\sigma^2}{2\sigma_s^2 + 3\sigma^2}\right)}_{w_2} (y_{41} - y_{31})$$

Weights depend on relative sizes of within- and between-subject variability

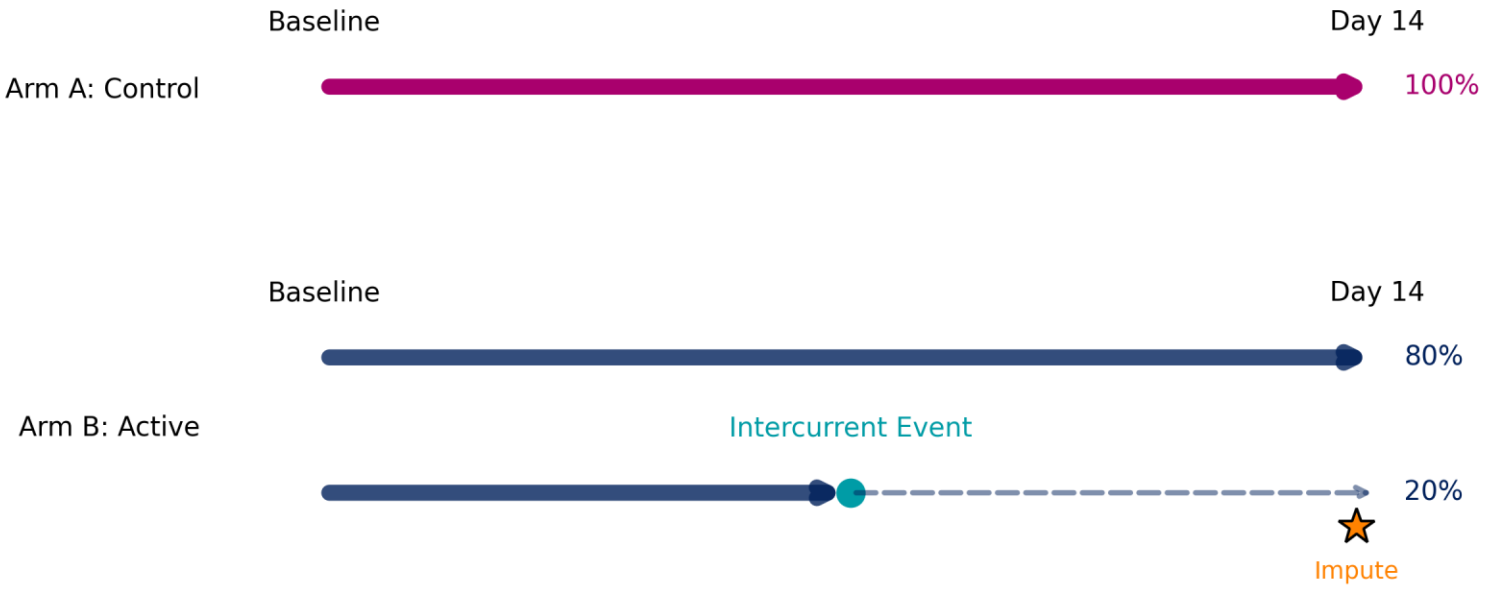
within-subject information

between-subject information

Note: A fixed subject model corresponds to an estimate based on within-subject information.

Composite approach in parallel arm trial

- Simple example for a parallel arm trial.



Effect: 0

Effect: 0.15

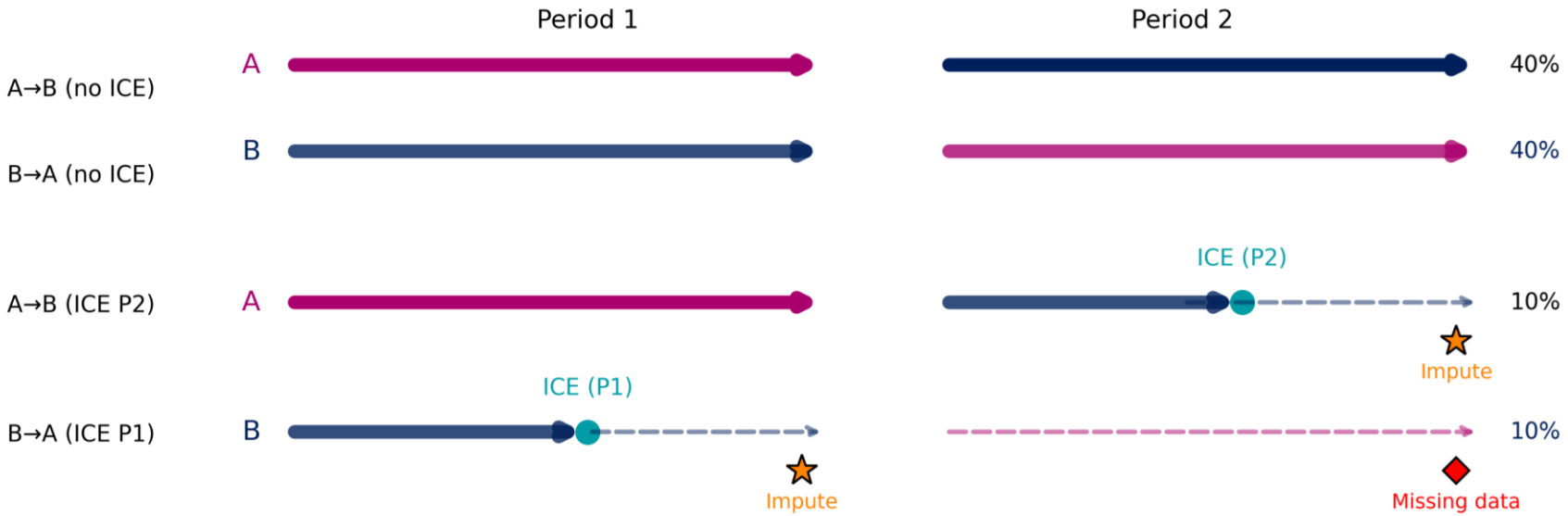
Effect: $1.4 \cdot -0.1 = -0.14$

Overall effect:

$$\underbrace{0.8 \cdot 0.15}_{0.12} + \underbrace{0.2 \cdot -0.14}_{-0.028} - 0 = 0.092$$

Composite approach in cross-over trial

- Example for a cross-over arm trial.



Baseline level: 1.4

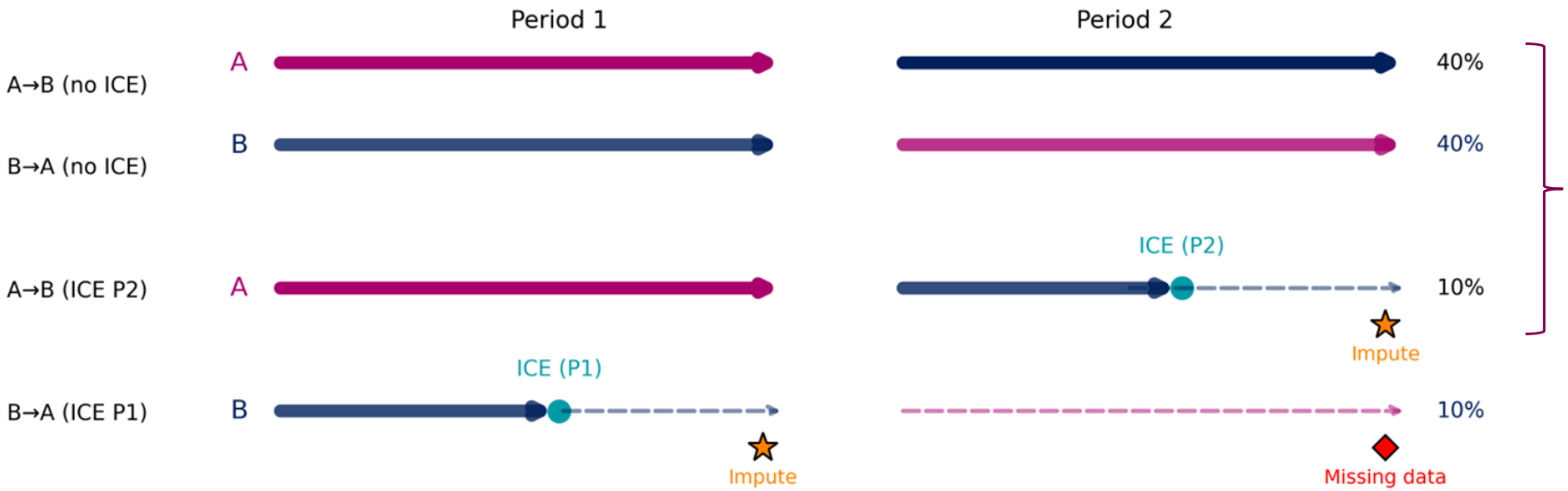
Imputed value:

10% drop from baseline

The expected effect of treatment A is 0, so does it matter that data is missing?

Yes!

Composite approach in cross-over trial: Expected effects



Within-subject effect:

$(0.8/0.9) \cdot (0.15 - 0) + (0.1/0.9) \cdot (-0.1 \cdot 1.4 - 0) \approx 0.118$

Between subject effect:

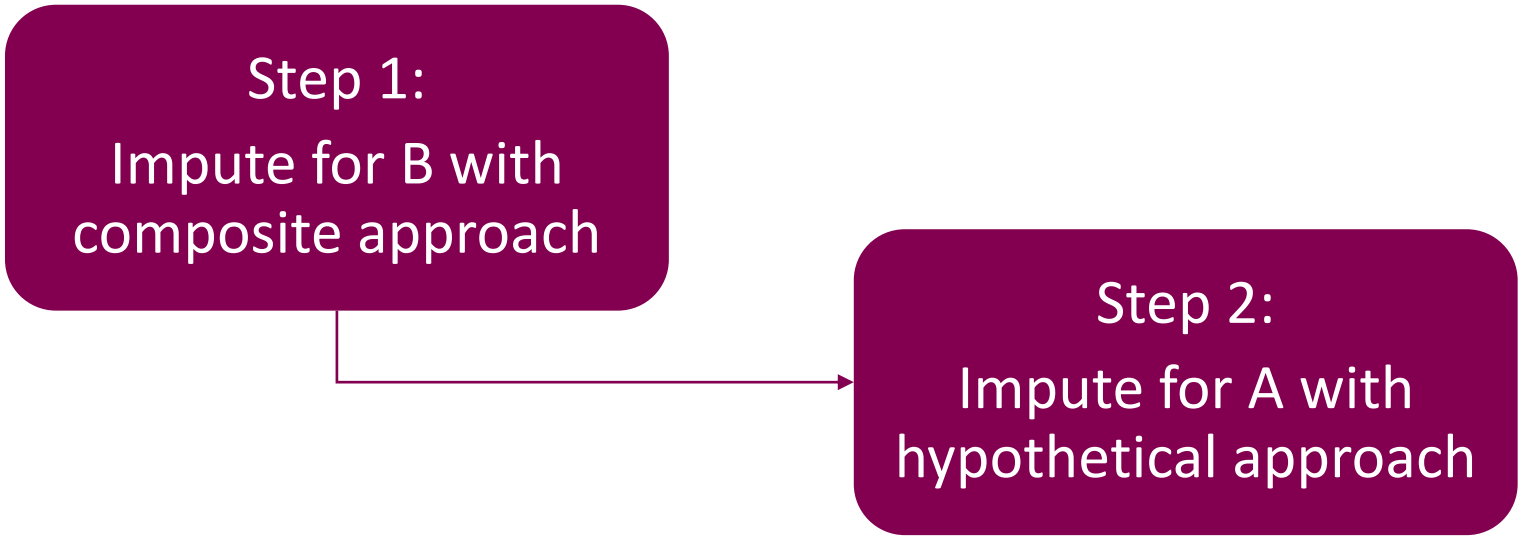
$1.4 \cdot -0.1 = -0.14$

Random subject model: expected effect will be > 0.092 but < 0.118

In cross-over trials, applying the composite handling strategy may not by itself be enough to target the intended estimand.

Composite estimand: Imputation approach

- Occurrence of the ICE is unrelated to treatment A: Impute data for A as if the ICE did not happen (hypothetical approach)



Mixed model with

- One effect for treatment of B (vs A) under no ICE.
- One effect for treatment of B (vs A) under ICE.

Needed to target the effect for the reference level (A).

Composite estimand: Simulation example

2x2 crossover trial with 20 subjects per sequence comparing treatments A and B.

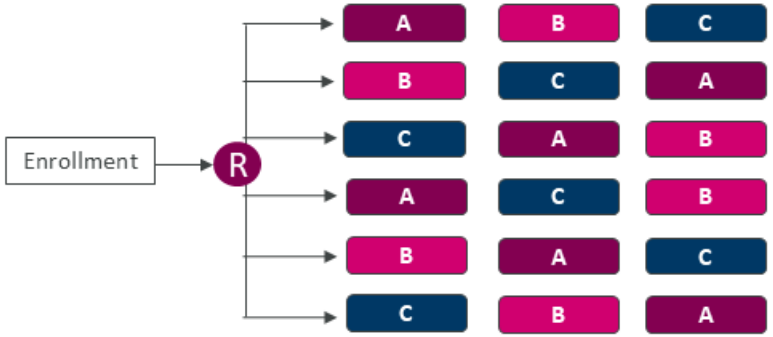
Design	Model	Imputation	Average effect
Cross-over	Random subject model	Composite for B	0.107
Cross-over	Fixed subject model$^{\$}$	Composite for B	0.120
Cross-over	Random subject model	Composite for B Hypothetical for A	0.092
Parallel	Linear model	Composite for B	0.092

Only the estimand-aligned approaches recover the target effect seen in the parallel trial analogue.

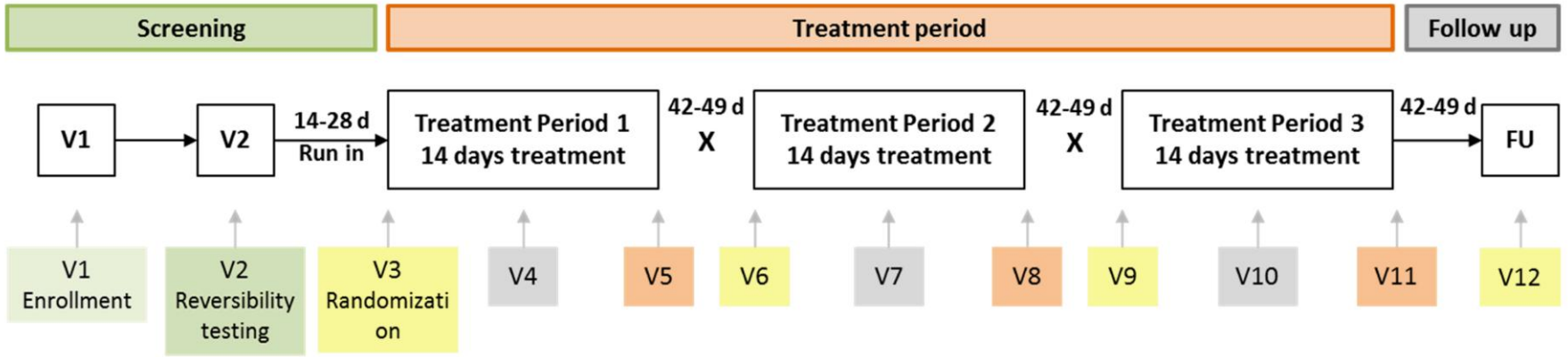
5,000 iterations with fixed effects (intercept 1.4, treatment effect 0.15) with simulation of baseline and post-baseline values. All models include change from first baseline as the response, baseline, period and treatment effects, except the parallel arm model which only includes treatment and baseline as covariates. 20% of subjects experiencing an intercurrent event (ICE) in treatment B. $: Using within-subject information only

Example: Williams design with 3 treatments

- Key objectives/endpoints: Lung function efficacy
- 3-period, 3-treatment Williams design (6 sequences)
  - 2 active treatments + placebo (A, B and C)
- Enrollment: 73 randomized; 66 completed all 3 periods



2 weeks treatment;
6–7 weeks wash-out

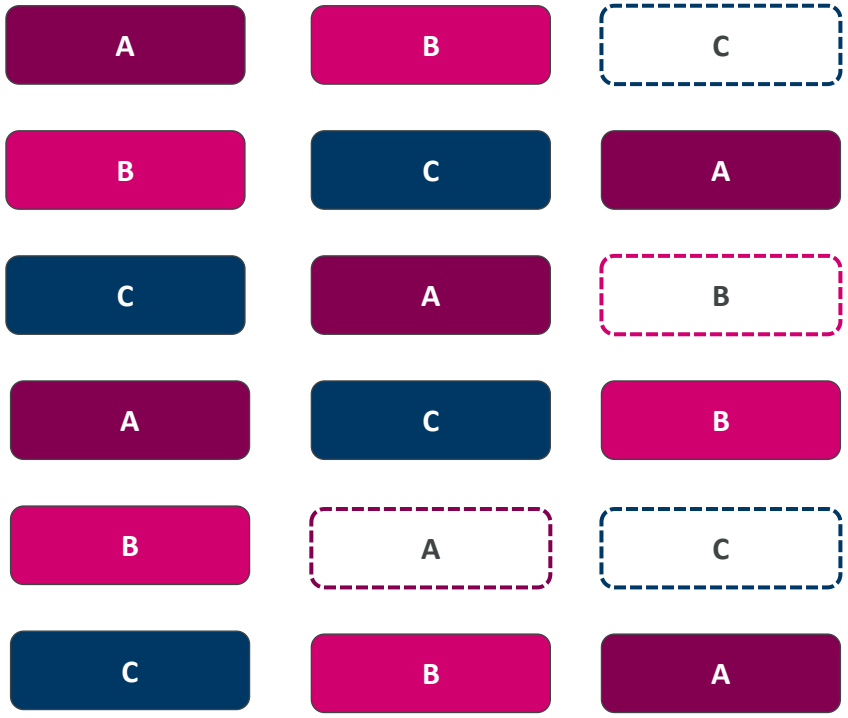


d: day; FU: Follow-up; V: Visit.

Dave Singh, Jutta Beier, Carol Astbury, Maria G Belvisi, Carla A Da Silva, Alexandra Jauhiainen, Eulalia Jimenez, et al. 2022. "The Novel Bronchodilator Navafenterol: A Phase 2a, Multicentre, Randomised, Double-Blind, Placebo-Controlled Crossover Trial in COPD." *Eur. Respir. J.* 59 (4): 2100972. https://doi.org/10.1183/13993003.00972-2021.

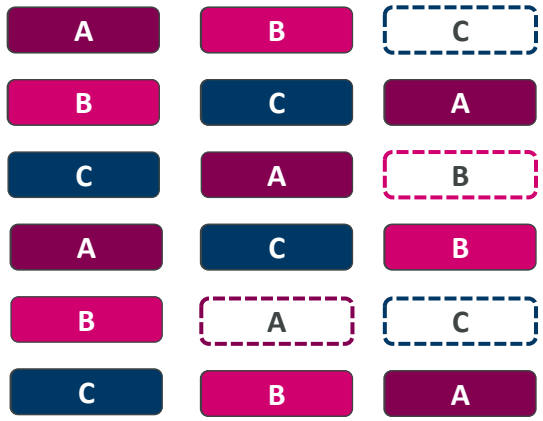
How do we target the treatment comparison A vs B among subjects that can tolerate both treatments?

- Available data (dashed treatment periods where treatment not tolerated and data is missing):

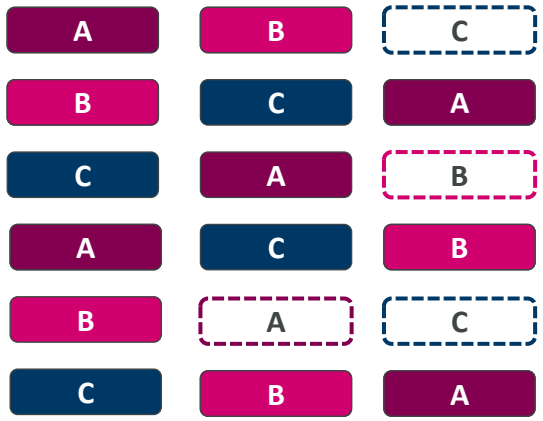


How do we target the principal stratum for A vs B?

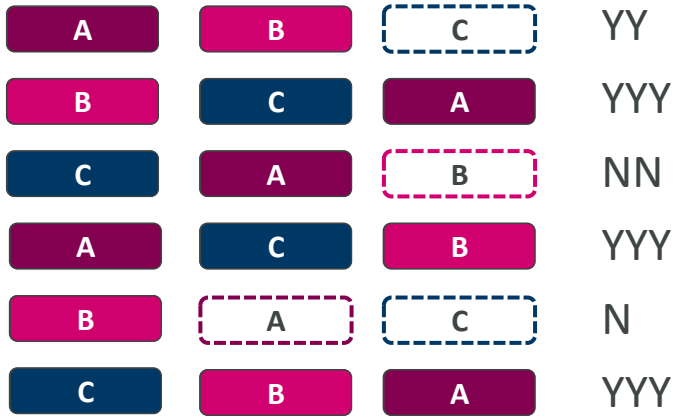
1. Filter to principal stratum



2. Filter to principal stratum treatments



3. Flag stratum and model treatment-by-stratum interaction

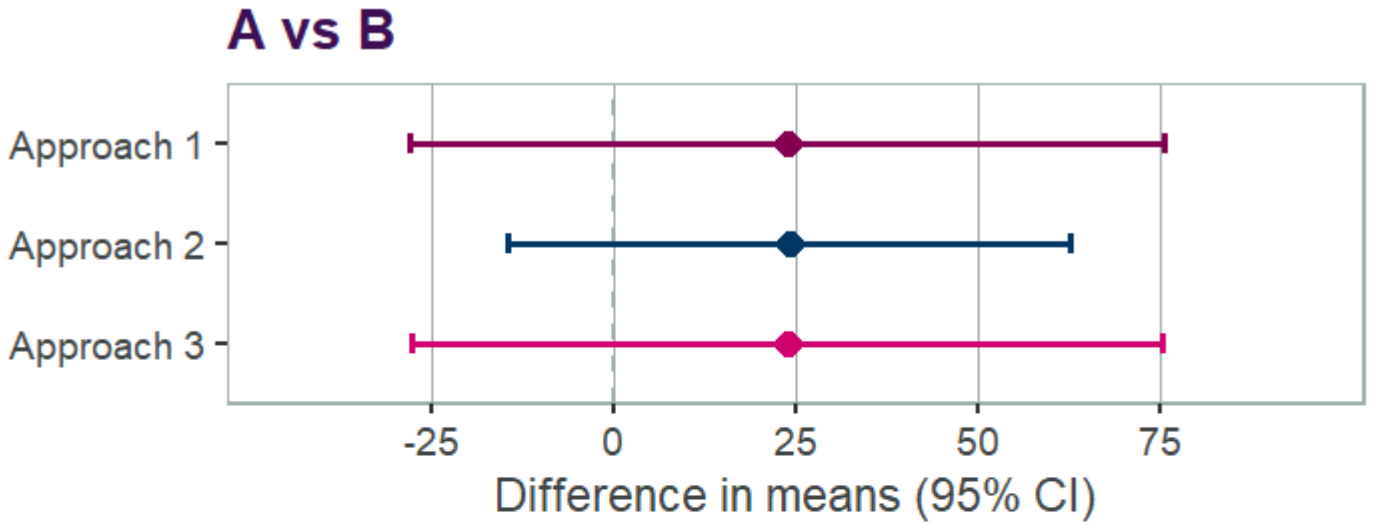


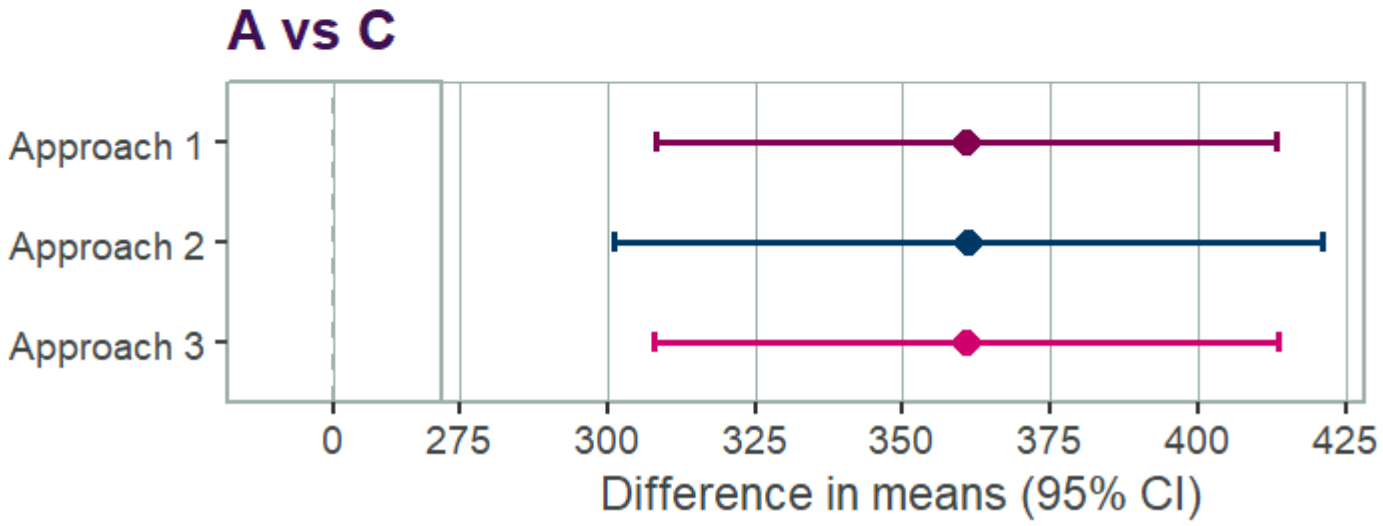
Filtering is intuitive but may lose balance/information

Interaction models use more data but can be harder to specify and fit

Example: Principal stratum, comparison of effects

- Effects similar across approaches (small amount of missing data)
- Filtering for principal stratum treatments may or may not be beneficial in terms of variability.





Endpoint: Change from first baseline in Peak FEV1 (ml). Random subject model used with effects for baseline, treatment (or treatment x stratum interaction), and period.

Conclusions

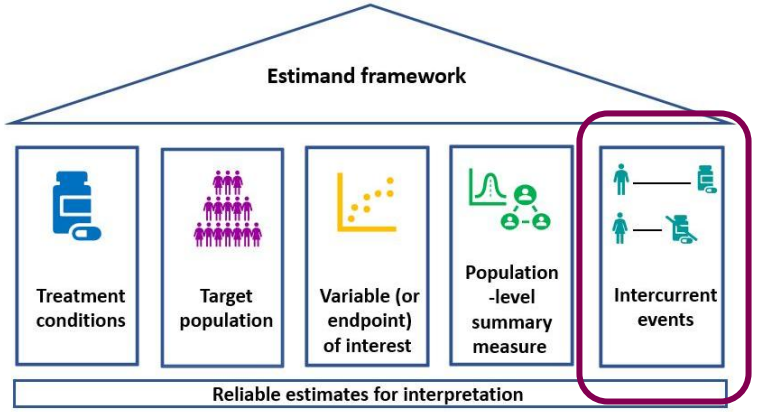
- Cross-over trials need estimand-led methods; standard analyses may not answer the intended treatment question.

  - First define the treatment question
  - Then specify how ICEs should be handled
  - Then choose the analysis method that actually targets that estimand in a cross-over setting.
    - Important to consider missing data for certain ICE handling approaches.

Additional slides

Estimands in the cross-over context

Estimand framework



- Efficacy trial: while-on-treatment, composite, treatment policy
- Clinical pharmacology trials: while-on-treatment, principal stratum

What's unique in cross-over?

- ICE in period j can remove or alter information for period $j + 1$ and affect other treatments.
- Estimand must handle this cross-period dependency for each treatment condition.
- Analysis model not just a technical choice, impacts whether the estimate matches the intended estimand.

Figure from J. Anzures-Cabrera, A. Monnet, G. Pagano. Improving the design of clinical trials in early-stage Parkinson's disease by using the estimand framework [abstract]. *Mov Disord.* 2022; 37 (suppl 2). https://www.mdsabstracts.org/abstract/improving-the-design-of-clinical-trials-in-early-stage-parkinsons-disease-by-using-the-estimand-framework/. Accessed April 27, 2026.

ICE handling strategies applicable in cross-over trials

Efficacy trial

"The FAS population is defined as all patients randomised and receiving IP, irrespective of their protocol adherence and continued participation in the study."

"Exclude data beyond study intervention discontinuation within period."

While-on-treatment

Treatment policy

Composite

Clinical pharmacology trial

"All subjects who received at least one dose of drug X and for whom at least one of the primary PK parameters could be calculated and who had no major protocol deviations thought to impact on the analysis of the PK data."

While-on-treatment

Principal stratum

Hypothetical

Summary of ICE handling strategies and targeting analyses

- While-on-treatment is usually straightforward with a random subject model.
- Hypothetical strategies generally need additional imputation.
- Principal stratum approaches require explicit stratum definition, such as filtering or treatment-by-stratum interaction.
- Composite / treatment policy handling can be more challenging in cross-over than in parallel designs. Post-ICE missing data may require combining the primary strategy with a hypothetical approach.

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