Risk of Bias Tool 2 for Crossover Trials

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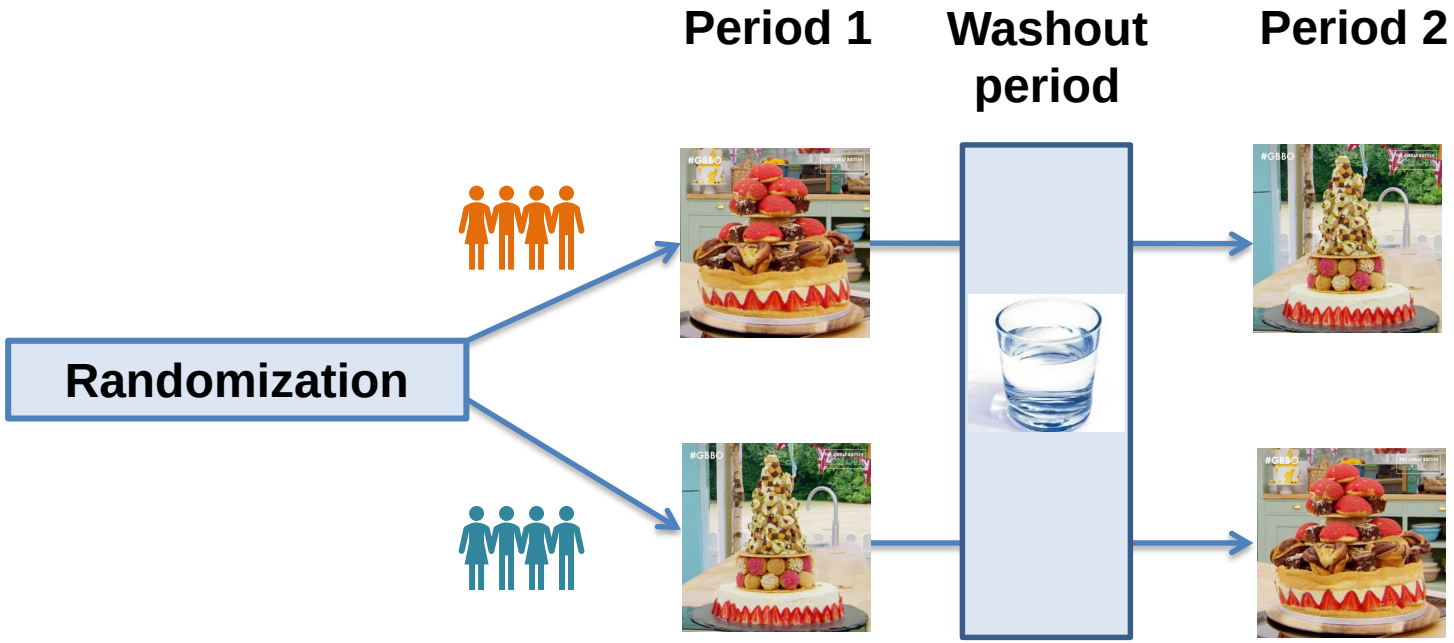
A parallel design to compare two cakes

Randomization

A crossover design to compare two cakes



Advantages and challenges of crossover design

Advantages

- Permits within-person comparisons
- Potential saving in sample size
- Allows assessment of preferences

Challenges

- Condition has to be suitable (e.g., chronic and stable)
- Treatment effect has to be reversible and temporary
- Issues with period effect and carryover effect

Senn 2002, Freeman 1989, Piantadosi 2005, Li 2015, Dwan 2019, Zheng 2020

Analysis of crossover trials should account for the paired design

	Period 1	Washout period	Period 2
Seq AB	A		B
Seq BA	B		A

	Participant ID	Period 1	Period 2	Within-person difference
		A	**B**	
Seq AB	1	Y_{1a}	Y_{1b}	$Y_{1a}-Y_{1b}$
	2	Y_{2a}	Y_{2b}	$Y_{2a}-Y_{2b}$
	3	Y_{3a}	Y_{3b}	$Y_{3a}-Y_{3b}$
		B	**A**	
Seq BA	4	Y_{4b}	Y_{4a}	$Y_{4a}-Y_{4b}$
	5	Y_{5b}	Y_{5a}	$Y_{5a}-Y_{5b}$
	6	Y_{6b}	Y_{6a}	$Y_{6a}-Y_{6b}$

Average within-person differences to estimate the relative effect between interventions with associated confidence interval.

An example of inappropriate analysis and reporting

TABLE 2. Mean Treatment Intraocular Pressures ± Standard Deviation (mm Hg)

n	Timolol/Dorzolamide Fixed Combination	Confidence Intervals	Unoprostone† Timolol	Confidence Intervals	*P* Value*
32	20.8 ± 4.1	19.3–22.3	20.1 ± 4.5	18.5–21.8	0.55

	Period 1		Period 2
Seq AB	A	ut period	B
Seq BA	B		A

Day 2003

An example of inappropriate analysis and reporting

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Unit of analysis error is **NOT** addressed in RoB 2

	Period 1		Period 2
Seq AB	A	Washout period	B
Seq BA	B		A

Day 2003

RoB 2 domains for crossover trials

Domain 1. Bias arising from the randomization process

Truly random sequence

Randomization

Concealment of allocation

Domain 2. Bias due to deviations from intended interventions

Period 1 | Washout | Period 2

Blinding of participants and experimenters

Domain 3. Bias due to missing outcome data

No omissions from analysis

Domain 4. Bias in measurement of the outcome

Outcome?

Blind assessment

Outcome?

Honest reporting

Domain 5. Bias in selection of the reported result

https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/rob-2-for-crossover-trials

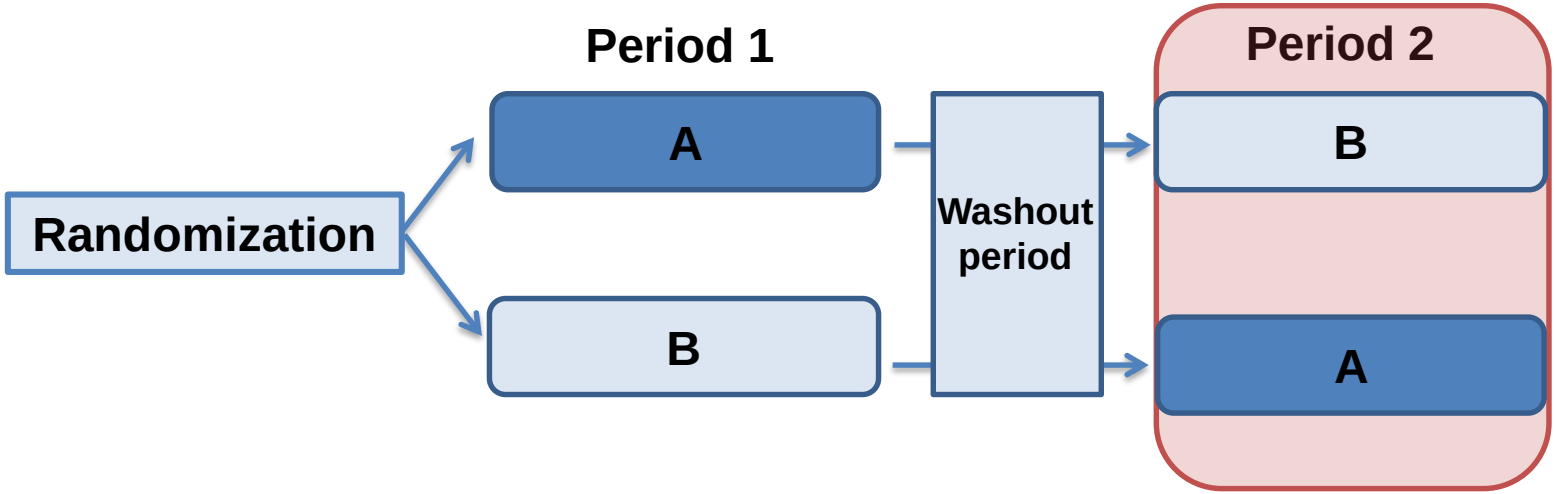
What's different for crossover trials?

Special considerations (Domain S): bias arising from period effect and carryover effect

https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/rob-2-for-crossover-trials

1. Period effect

A general tendency that even if the participants were given identical interventions in both periods, values in the second period would be always higher (or always lower) than those in the first.



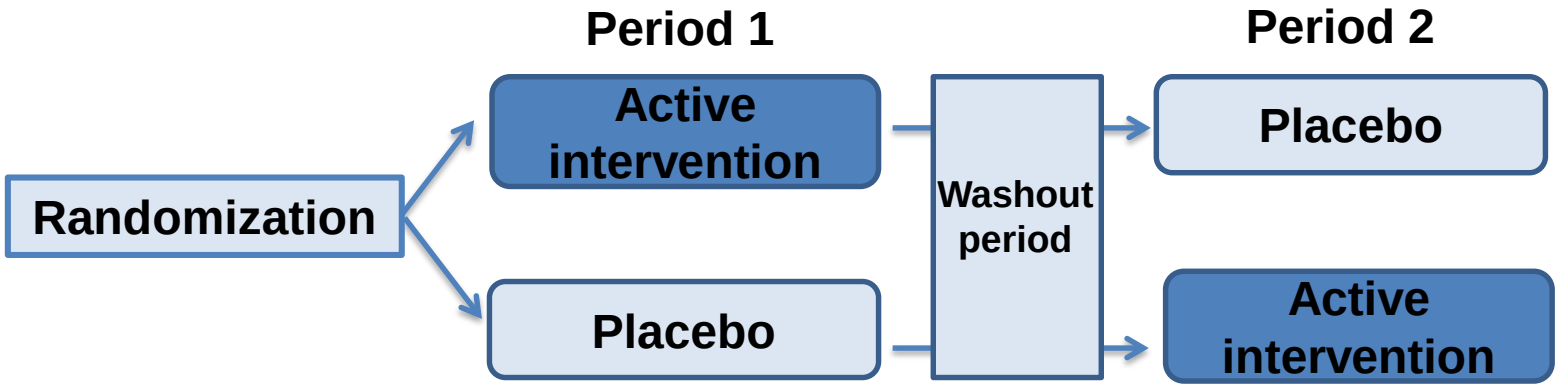
Senn 2002, Freeman 1989, Piantadosi 2005, Li 2015, Dwan 2019, Zheng 2020

Assessing RoB due to period effect

Signalling questions	Additional issues addressed compared with parallel-group trials
Was the number of participants allocated to each of the two sequences equal or nearly equal?	If the allocation ratio is 1:1, then any general trends in outcomes over time (that is, **period effects**) will cancel. • Y/PY -> low risk of bias • N/PN/NI-> A general trend in outcomes over time may lead to bias. For example, if there is a general deterioration in outcomes, imbalance in numbers will lead to bias against the intervention that is "over-represented" in the second period.
If N/PN/NI: Were period effects accounted for in the analysis?	If **period effects** are included in the analysis-> low risk of bias If **period effects** are present but not included in the analysis, then there is a risk of bias.

2. Carryover effect

Carryover effect occurs when the intervention from one period has a residual effect that persists into the subsequent period.

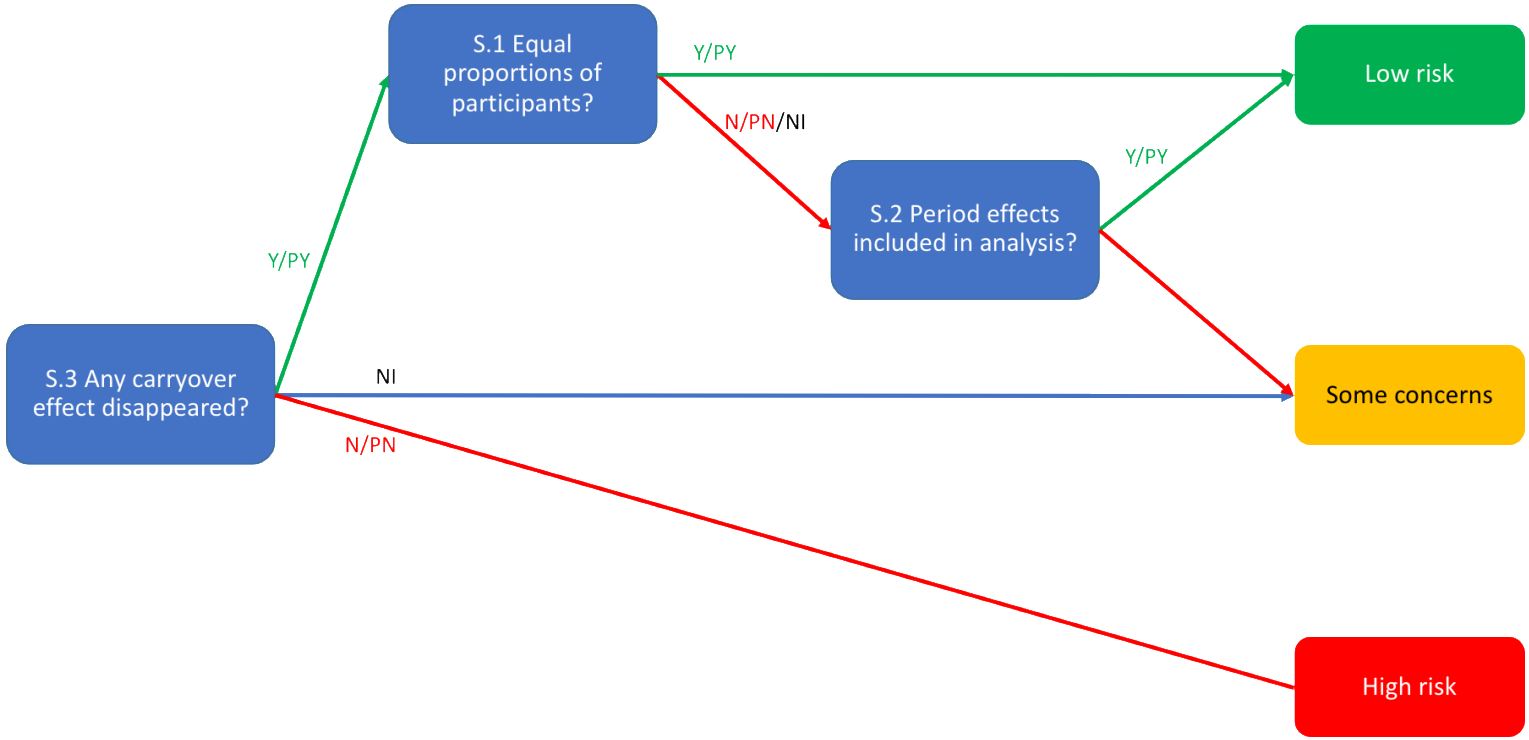


Senn 2002, Freeman 1989, Piantadosi 2005, Li 2015, Dwan 2019, Zheng 2020

Assessing RoB due to carryover effect

Signalling questions	Additional issues addressed compared with parallel-group trials
Was there sufficient time for any carryover effects to have disappeared before outcome assessment in the second period?	**Carryover effects** should not affect outcomes measured in the second period. A long wash-out between periods can avoid this. The important consideration is whether sufficient time passes before outcome measurement in the second period, such that any carry-over effects have disappeared.

Suggested algorithm for reaching risk of bias judgements for bias arising from period and carryover effects in a crossover trial



Implications of analyzing within-person difference

- Balance assessed between interventions (rather than between sequences)
  - Domain 2: bias due to deviations from intended interventions
  - Domain 3: bias due to missing outcome data

Example 1	Period 1	Period 2
Seq AB	A (30%)	B (30%)
Seq BA	B	A

Example 2	Period 1	Period 2
Seq AB	A (10%)	B (30%)
Seq BA	B (10%)	A (30%)

Which RoB 2 tool to use?

Scenario	RoB 2 for crossover trials	RoB 2 for parallel group trials
Data from both periods have been analysed appropriately	✓	
Data from both periods have been analysed **in**appropriately	✓	
Data from the first period only have been analysed	✓	✓

Consider the possibility that the reported result (from the first period alone) was selected because it was preferred to a result based on both periods within signalling question 5.3 of the main tool (*Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible analyses of the data?*).

RoB 2 domains for crossover trials

Domain S: bias arising from period effect and carryover effect

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Outcome?

Outcome?

Domain 5. Bias in selection of the reported result

Honest reporting

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