Statistical Methods for Innovative Platform Trial Designs Incorporating Non-concurrent Controls

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Adaptive platform trials

Multi-arm multi-stage trials that allow new experimental treatment arms to enter and leave the trial at different times.[1]

- Treatments to be studied not defined upfront
- Control arm can be shared

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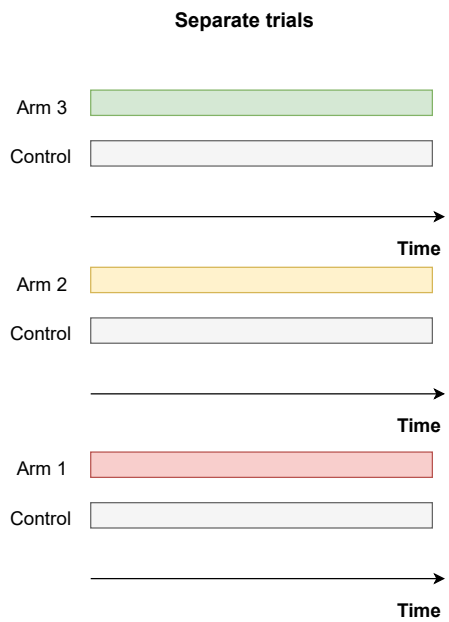

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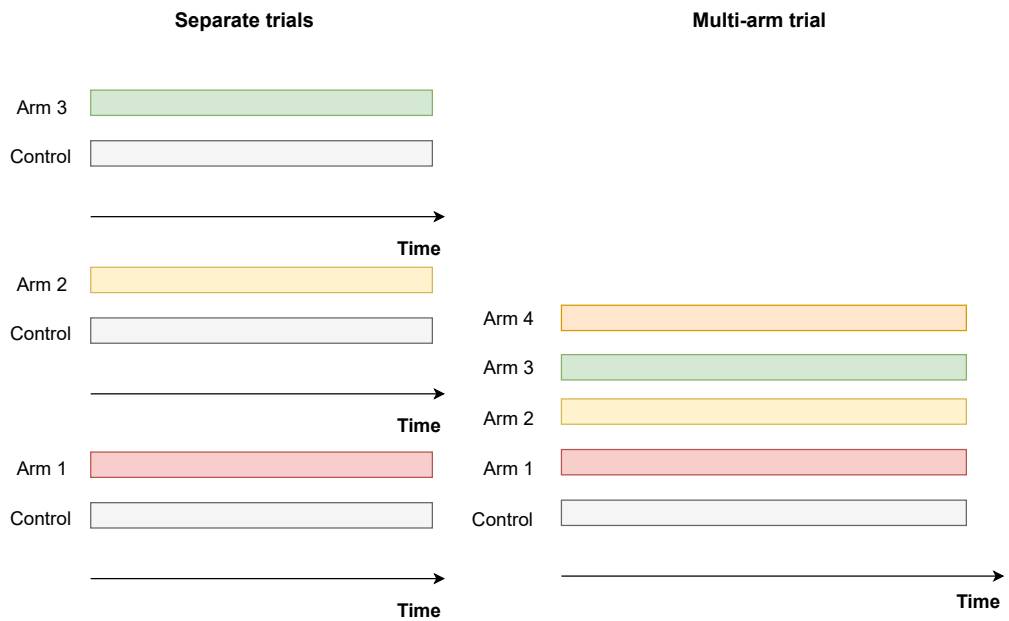

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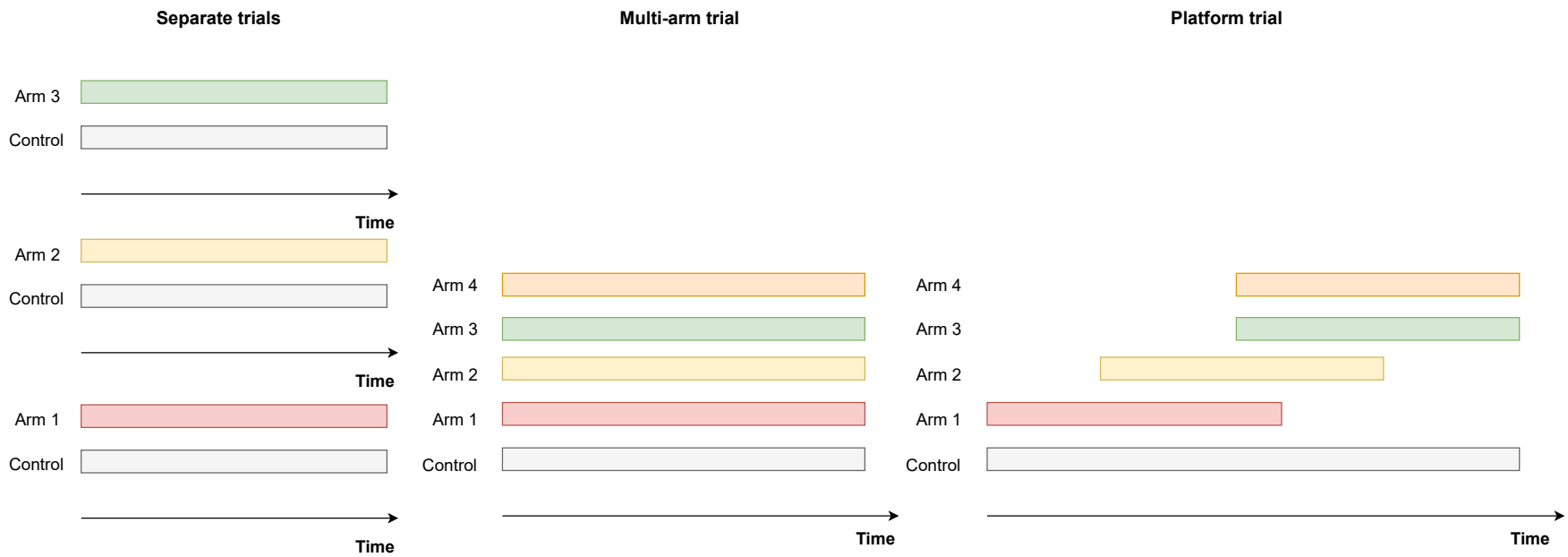

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Adaptive platform trials

Benefits:

- Treatments are evaluated **faster** as compared to separate trials since drugs are tested **in parallel**
- Trials are **more efficient** due to the joint trial infrastructure
- **Less patients** are required in the control group as it is shared across all treatment arms
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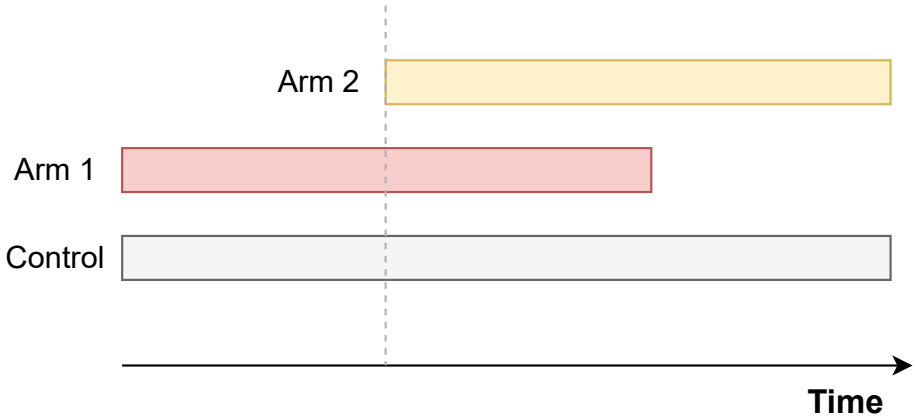
Challenges:

- Multiple operational and statistical challenges due to **higher complexity**
- Adaptations to the trial (e.g. entering and leaving times or the total number of experimental treatments) are **unknown in advance**
- Use of the **shared control arm** in trial analysis

Control groups in platform trials

Concurrent and non-concurrent controls

- **Concurrent controls (CC):** patients recruited to the control when the experimental treatment is part of the platform
- **Non-concurrent controls (NCC):** patients recruited before the experimental treatment entered the platform



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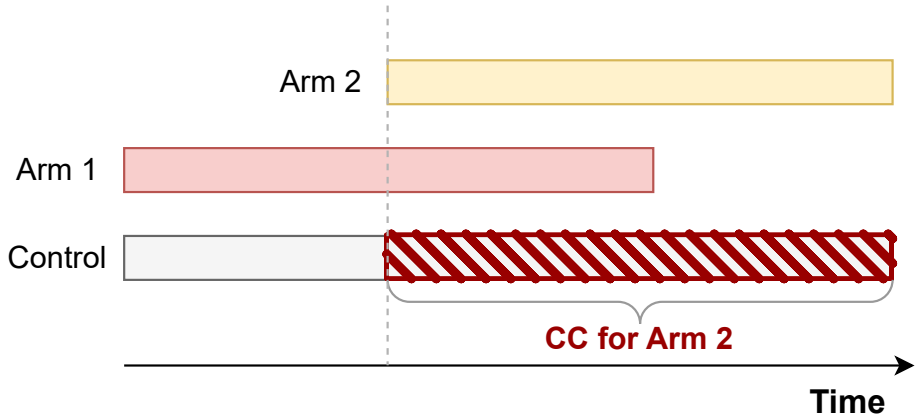

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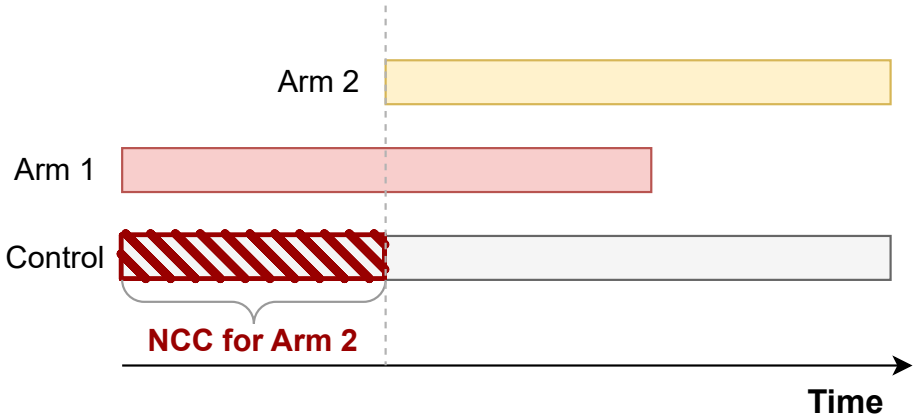

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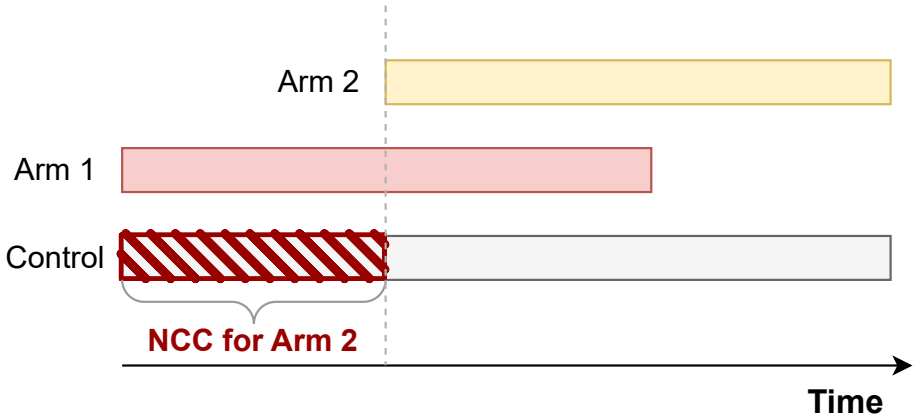

Hypothesis testing problem:

$$H_0 : \theta_2 = 0$$
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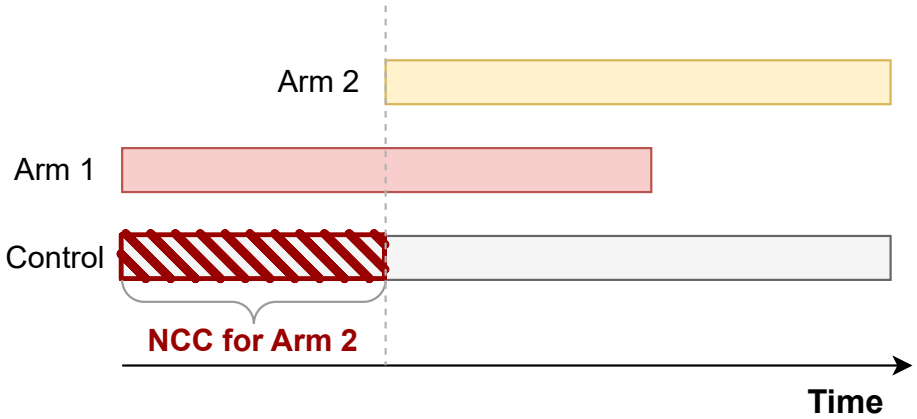

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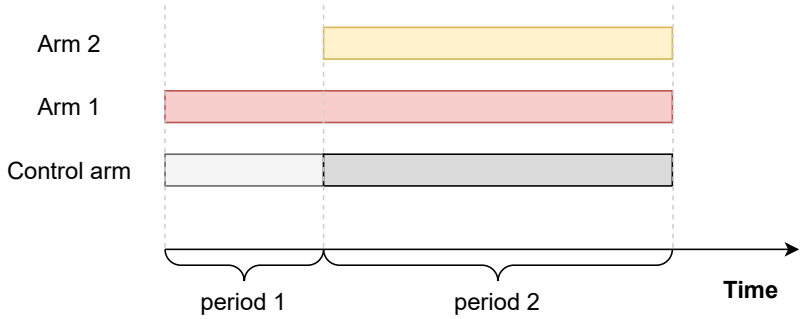
Challenges when using NCC in the presence of time trends[2]:

- Bias in the estimates
- Type I error rate control

[2] Dodd, L. E., et al. (2021). Platform Trials — Beware the Noncomparable Control Group. New England Journal of Medicine.

State-of-the-art analysis methods



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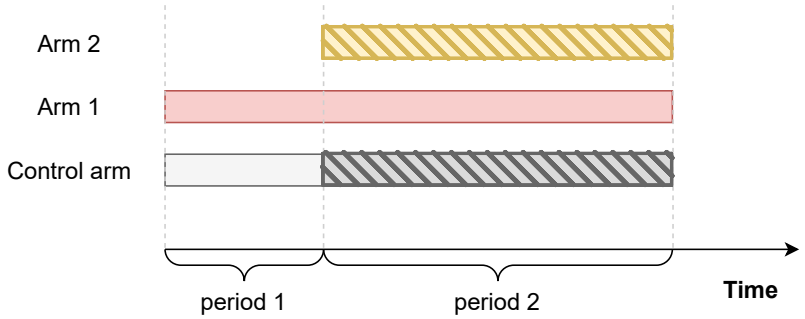

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Simple analysis methods

- **Separate approach:** analysis using only concurrent controls

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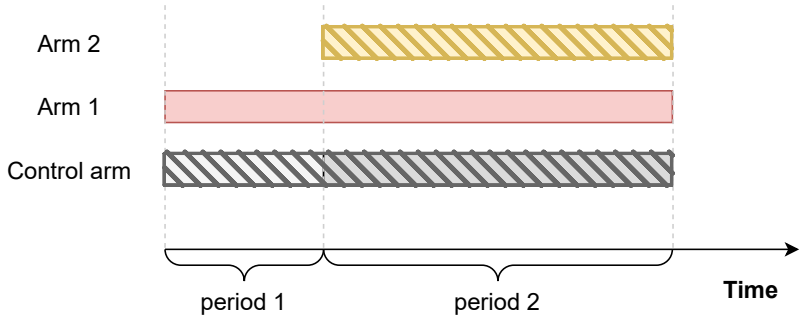

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- **Pooled approach:** pooling concurrent and non-concurrent controls

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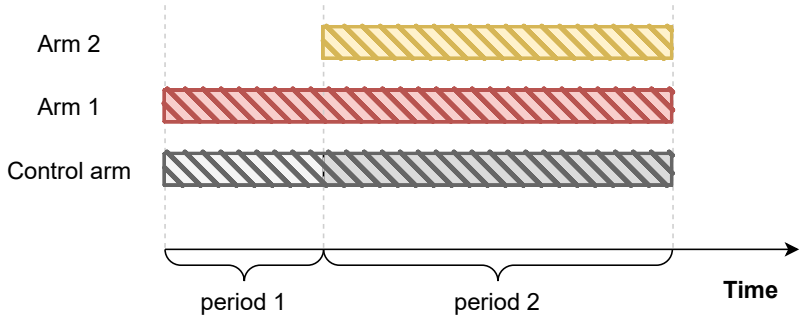

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Modelling approaches with time trend adjustment

- **Frequentist regression models:** adjust for time trends by including the factor period as a fixed effect (Lee & Wason, 2020; Bofill Roig, Krotka, et al., 2022)
- **Bayesian Time Machine:** adjusts for time by smoothing over calendar time intervals with a Bayesian normal dynamic linear model (Saville, et al., 2022)

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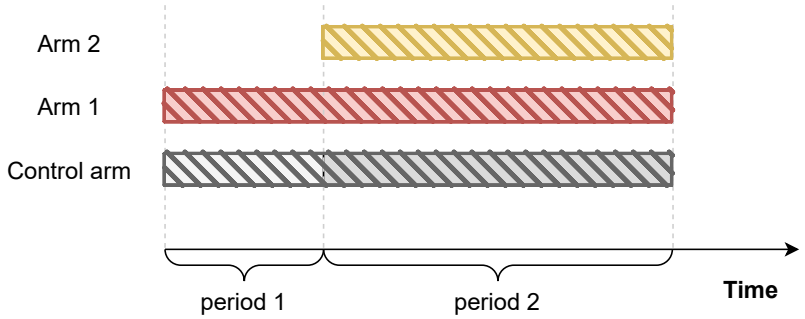

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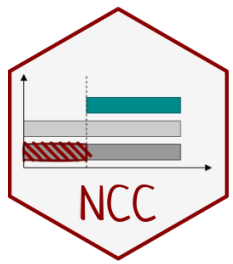
`NCC` R-package

- Software implementation of methods for incorporating NCC (Krotka, et al., 2023)
- Accompanying website: `https://pavlakrotka.github.io/NCC/`



Goals of the PhD thesis

1. Methodology for incorporating non-concurrent controls in trials with continuous endpoints and interim analyses

2. Extension of the methodology for including non-concurrent controls to trials with time-to-event endpoints

3. Methods for adaptive group-sequential trial designs utilizing pseudo-values regression

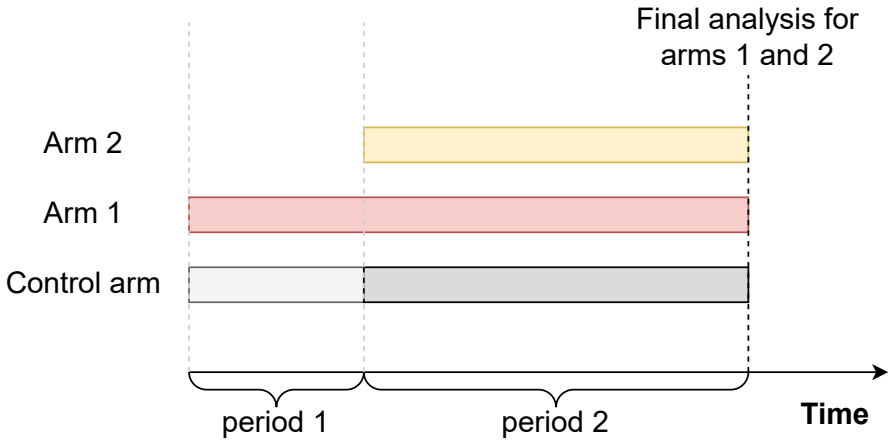
4. Software implementation in the `NCC` R-package

Objective 1

Incorporating non-concurrent controls in trials with interim analyses

Frequentist regression model

Without interim analysis in arm 1



Hypothesis testing problem:

$$H_0 : \theta_2 = 0$$
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Model-based approach[3] based on data from all treatment arms and control:

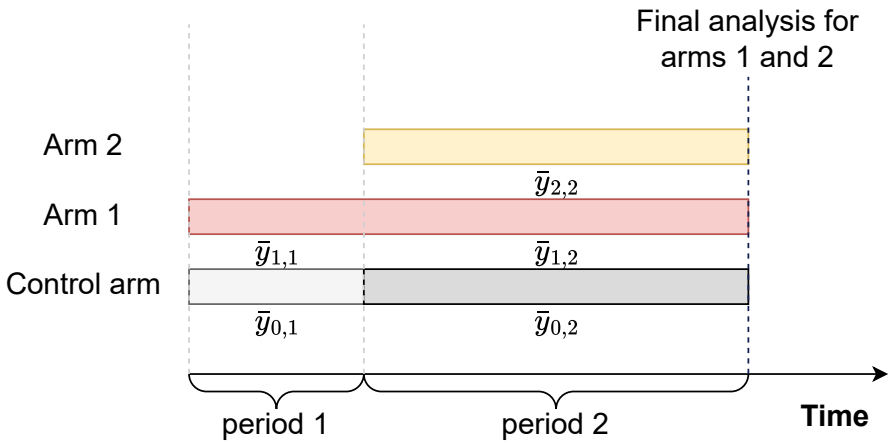
$$E(y_j) = \underbrace{\eta_0}_{\substack{\text{Control response} \\ \text{in period 1}}} + \underbrace{\sum_{k=1,2} \theta_k \cdot I(k_j = k)}_{\text{Treatment effects}} + \underbrace{\tau \cdot I(s_j = 2)}_{\text{Period time effect}}$$

where y_j is the outcome, $k = 0, 1, 2$ denotes the treatment and $s = 1, 2$ the period.

[3] Bofill Roig, M., Krotka, P., et al. (2022). "On model-based time trend adjustments in platform trials with non-concurrent controls." BMC Medical research methodology.

Estimation of treatment effect in arm 2 using regression methods

Without interim analysis in arm 1



$$\varrho = \frac{\frac{1}{n_{0,2}}}{\frac{1}{n_{0,1}} + \frac{1}{n_{0,2}} + \frac{1}{n_{1,1}} + \frac{1}{n_{1,2}}}$$

Treatment **effect estimator** using the model-based approach:

$$\tilde{\theta}_2 = \bar{y}_{2,2} - \tilde{y}_{0,2}$$

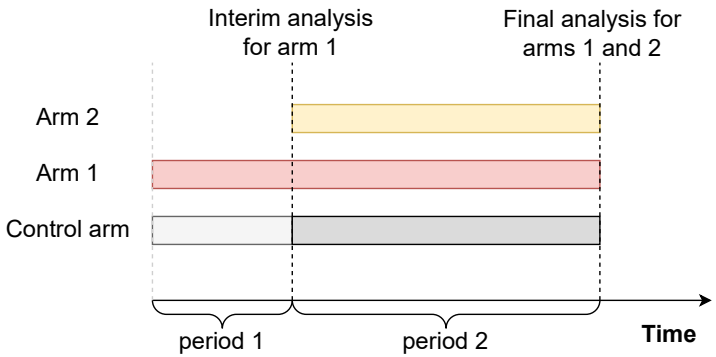
Model-based estimate of the **control response** in period 2:

$$\tilde{y}_{0,2} = (1 - \varrho) \cdot \bar{y}_{0,2} + \varrho \cdot [\bar{y}_{0,1} + \underbrace{(\bar{y}_{1,2} - \bar{y}_{1,1})}_{\text{Time trend estimate}}]$$

Model-based approach leads to an **unbiased treatment effect estimator** $\tilde{\theta}_2$ if the time trends in all arms are equal and additive on the model scale.

Platform trials with group sequential interim analyses

Interim analysis in arm 1 at the entry time of arm 2



Hypothesis testing problem:

Arm 1:

$$H_0 : \theta_1 = 0$$
$$H_1 : \theta_1 > 0$$

Interim analysis of arm 1:

Linear regression model without time adjustment:

$$E(y_j) = \underbrace{\eta_0}_{\text{Control response}} + \underbrace{\theta_1 \cdot I(k_j = 1)}_{\text{Treatment effect}}$$

- Stop arm 1 for futility if the one-sided p-value $p > \alpha_1$

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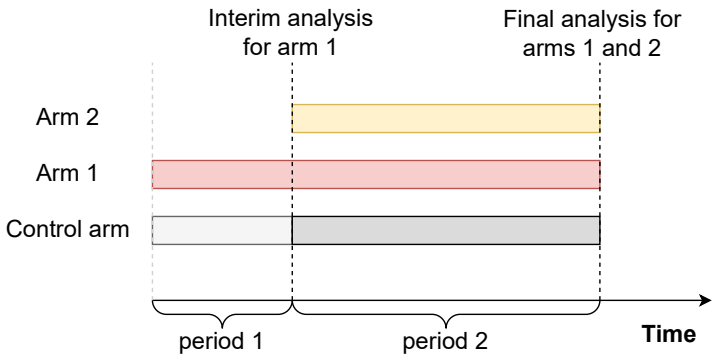

Hypothesis testing problem:

Arm 1:

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Arm 2:

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Analysis of arm 2:

Model-based approach including non-concurrent controls and adjusting for periods:

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Estimation of treatment effect in arm 2

Interim analysis in arm 1 at the entry time of arm 2

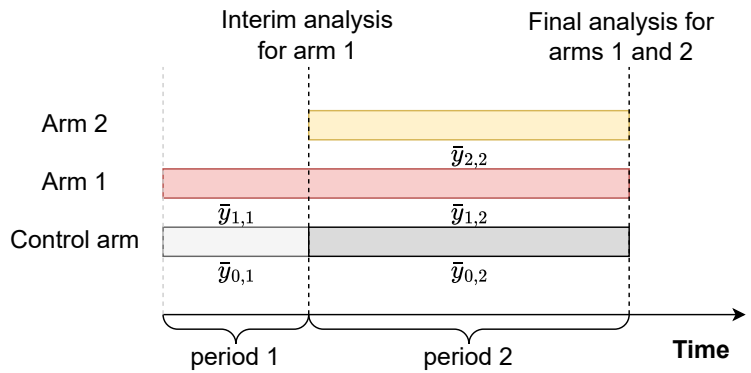
Treatment **effect estimator** for arm 2: $\tilde{\theta}_2 = \bar{y}_{2,2} - \tilde{y}_{0,2}$

Estimate of the **control response** in period 2:

If arm 1 **continues** at interim:

$$\tilde{y}_{0,2} = (1-\varrho)\cdot \bar{y}_{0,2} + \varrho \cdot [\bar{y}_{0,1} + \underbrace{\bar{y}_{1,2} - \bar{y}_{1,1}}_{\text{Time trend estimate}}]$$

$$\varrho = \frac{\frac{1}{n_{0,2}}}{\frac{1}{n_{0,1}} + \frac{1}{n_{0,2}} + \frac{1}{n_{1,1}} + \frac{1}{n_{1,2}}}$$



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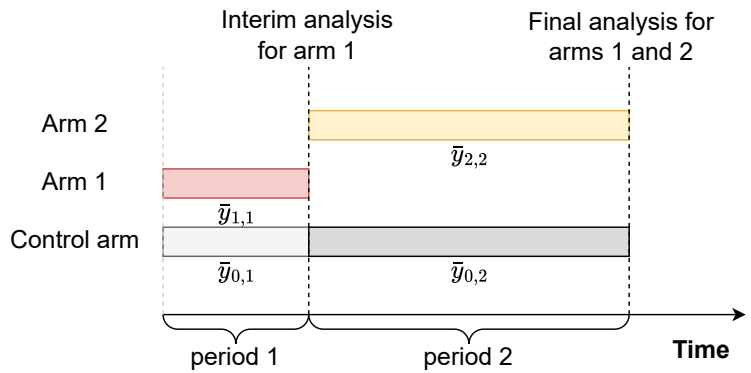
Note: if $n_{1,2} = 0$, $\varrho = 0$

If arm 1 **stops** at interim:

$$\tilde{y}_{0,2} = \bar{y}_{0,2}$$



If **arm 1 stops at interim**, the model-based approach does **not use non-concurrent controls**.

What is the impact of the futility bound α_1 on the type I error of arm 2?

Simulation setting

- $\theta_1 = \theta_2 = 0$
- Sample sizes of 250 for arm 1 and control; and 150 for arm 2
- Varying futility bound α_1

What is the impact of the futility bound α_1 on the type I error of arm 2?

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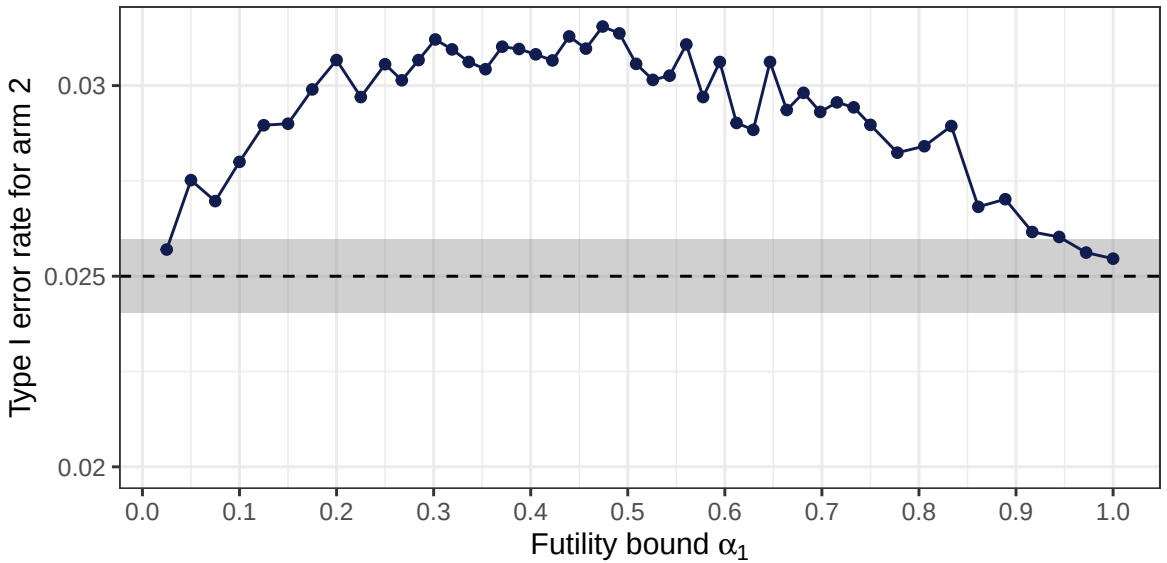

Type I error rate control of treatment arm 2 is **lost** if treatment arm 1 can be dropped at the interim analysis.

What is the impact of the effect θ_1 on the type I error of arm 2?

Simulation setting

- $\theta_2 = 0$
- Sample sizes of 250 for arm 1 and control; and 150 for arm 2
- Stopping for futility using futility boundary $\alpha_1 = 0.5$
- Stopping for efficacy using O'Brien-Fleming boundaries
- Varying the treatment effect θ_1 of treatment arm 1

What is the impact of the effect θ_1 on the type I error of arm 2?

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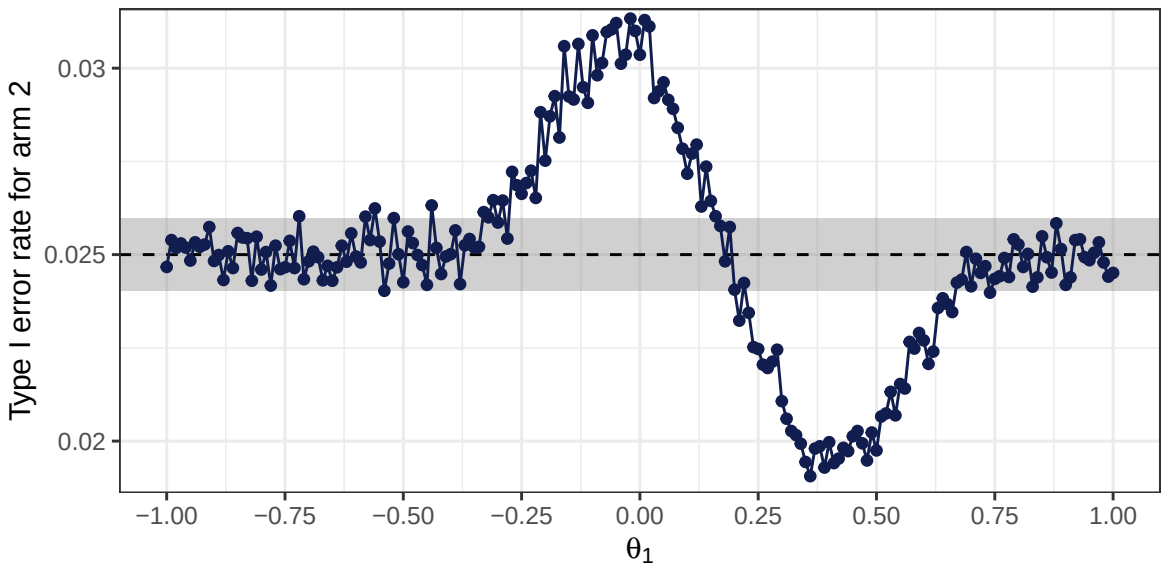

The **type I error rate** of treatment arm 2 is **inflated** for treatment effects of arm 1 around 0 and **deflated** in case of θ_1 around 0.4.

Summary

Key message

Including **interim analyses** to platform trials with non-concurrent controls leads to a **loss of type I error rate control** when using the regression model.

Next steps

- Evaluate the **maximum type I error rate inflation** in platform trial designs with interim analyses
- Propose **adjusted estimators** allowing for inclusion of NCC data, which either **eliminate** bias or **reduce** the bias
- Derive the **variance** of such estimators for conducting statistical tests

Selected references

- Bofill Roig, M., Krotka, P., Burman, C. F., Glimm, E., Gold, S. M., Hees, K., Jacko P., Koenig F., Magirr D., Mesenbrink P., Viele K., Posch, M., *"On model-based time trend adjustments in platform trials with non-concurrent controls."* BMC Medical research methodology 22.1 (2022): 1-16

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Thank you for your attention!

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