Maximizing efficiency in platform trials with shared controls

Optimal allocation strategies and non-concurrent controls

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MEDICAL UNIVERSITY
OF VIENNA

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"Optimal allocation strategies in platform trials". (2023) M. Bofill Roig, E. Glimm, T. Mielke, and M. Posch. *arXiv:2304.03035 [stat.ME]*

EU-PEARL (EU Patient-cEntric clinicAl tRial pLatforms) project has received funding from the Innovative Medicines Initiative (IMI) 2 Joint Undertaking (JU) under grant agreement No 853966. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA and Children's Tumor Foundation, Global Alliance for TB Drug Development non-profit organisation, Springworks Therapeutics Inc.

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

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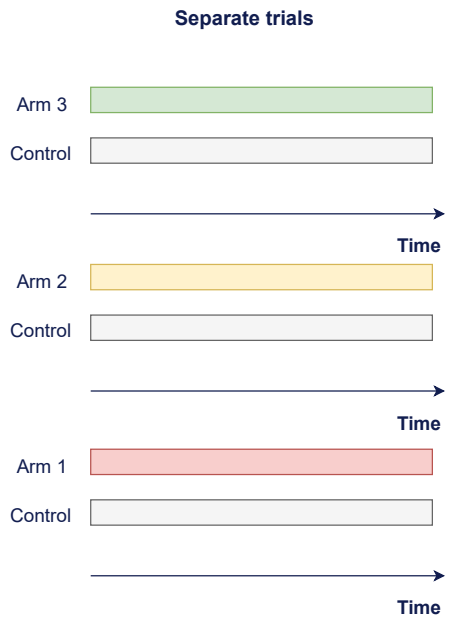

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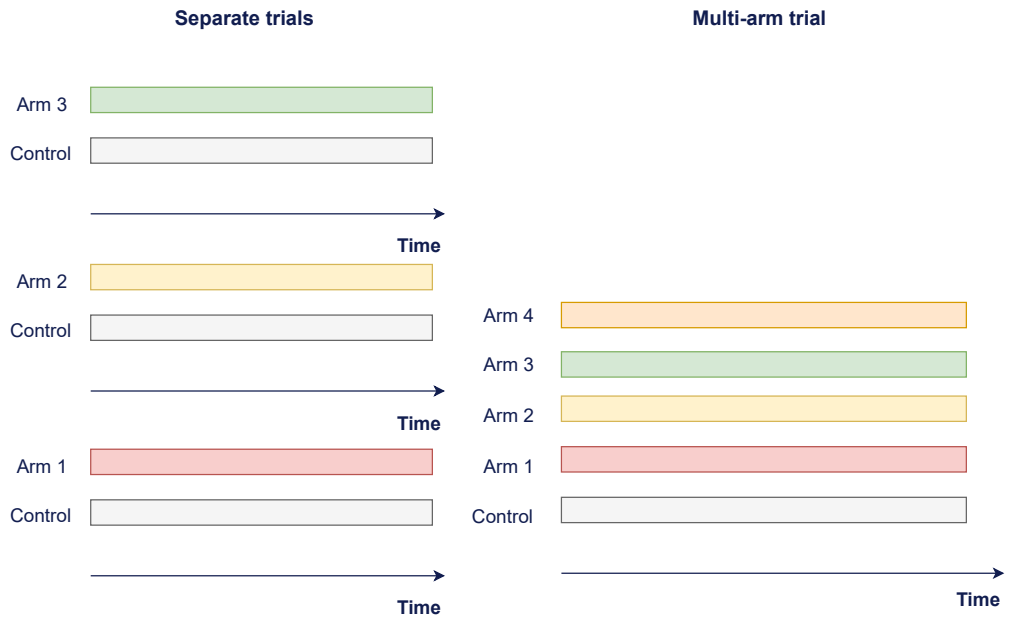

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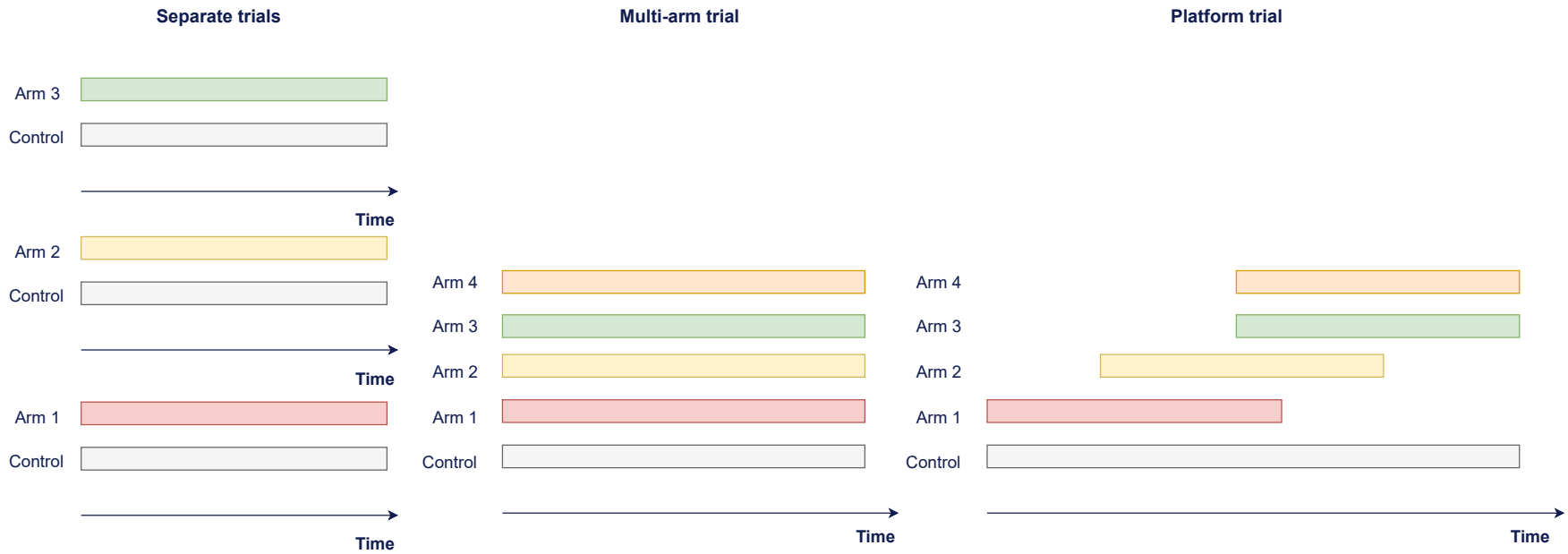


Potential sources of efficiency gains:

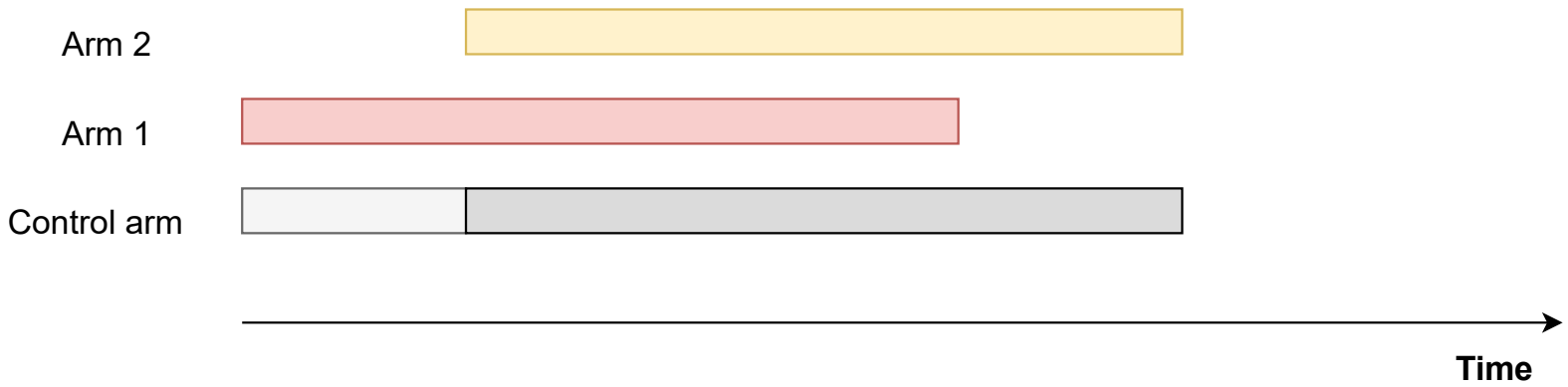
Use of shared controls and optimisation of allocation rates.

[1] Woodcock & LaVange (2017). Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both. NEJM

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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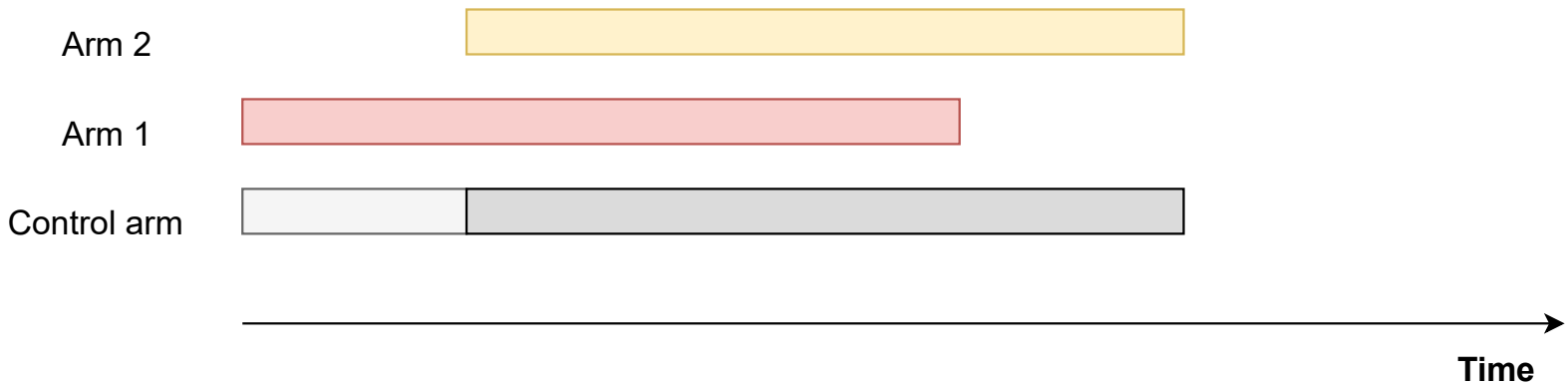

NCC have been **randomized** but at different calendar times.

Incorporating non-concurrent controls can increase the power of hypothesis tests and precision of estimates but may introduce bias due to **time trends**.

Analysis methods for trials with non-concurrent controls

Separate approach: Analysis using only concurrent controls.

Pooled approach: Analysis using concurrent and non-concurrent controls.

Model-based approach[1,2]:

Adjusts for time trends by including time as a covariate in a regression model.

[1] Lee, K. M., Wason, J. (2020). Including non-concurrent control patients in the analysis of platform trials: Is it worth it? BMC Medical Research Methodology

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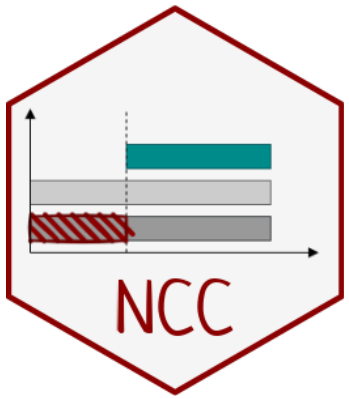
Session C14
Statistical modeling to adjust for time trends in platform trials utilising non-concurrent controls.
Pavla Krotka



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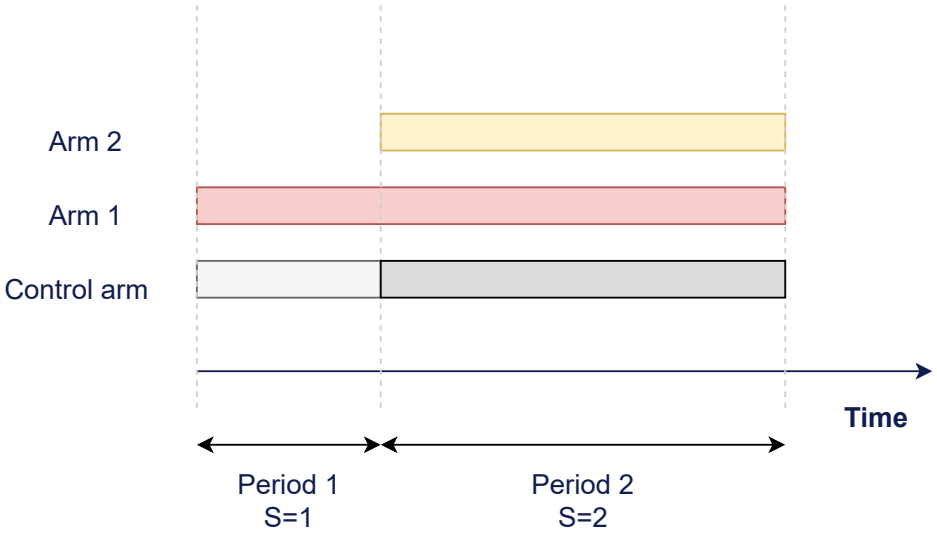
Frequentist regression methods



Hypothesis testing problem:

$$H_0 : \theta_2 = 0$$
$$H_1 : \theta_2 > 0$$

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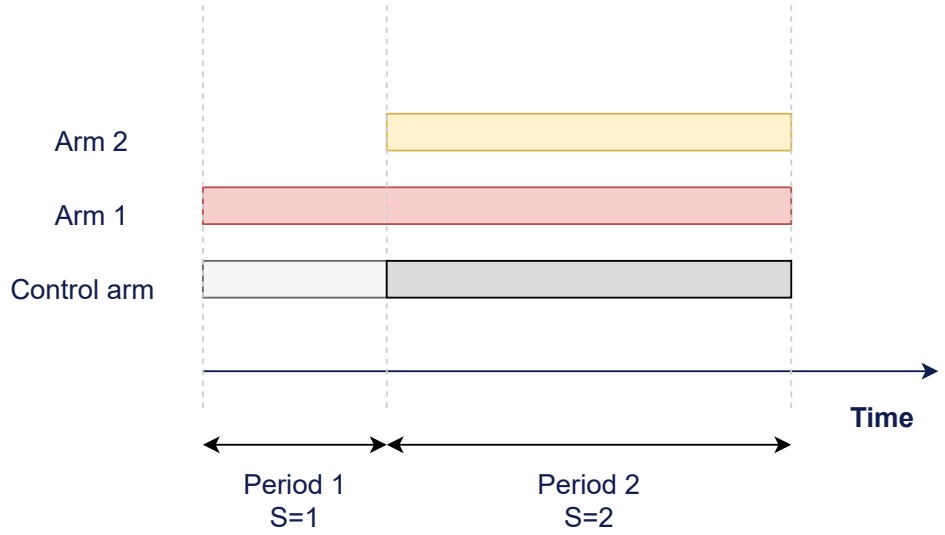


Hypothesis testing problem:

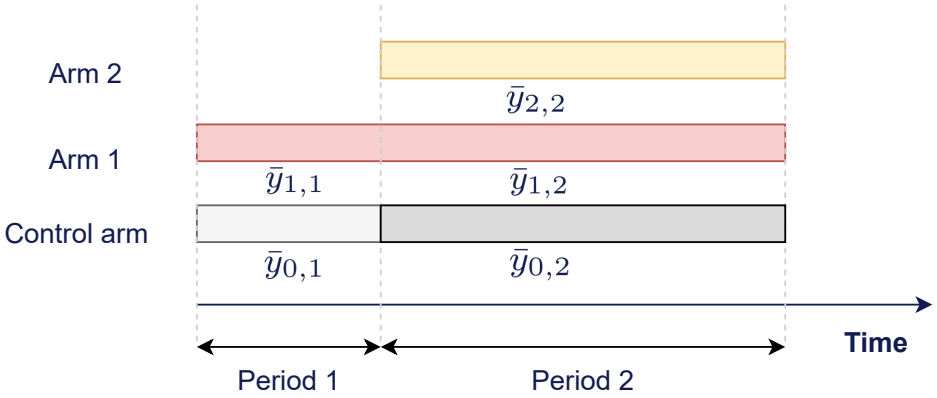
$$H_0 : \theta_2 = 0$$
$$H_1 : \theta_2 > 0$$

Model-based approach based on data from all treatment arms and control:

$$E(Y) = \underbrace{\eta_0}_{\text{Control response}} + \underbrace{\sum_{k=1,2} \theta_k \cdot I(T = k)}_{\text{Treatment effects}} + \underbrace{\tau \cdot I(S = 2)}_{\text{Period time effect}}$$

where Y is the outcome, $T = 0, 1, 2$ denotes the treatment and $S = 1, 2$ the period.

Estimation of treatment effect in arm 2 using regression methods



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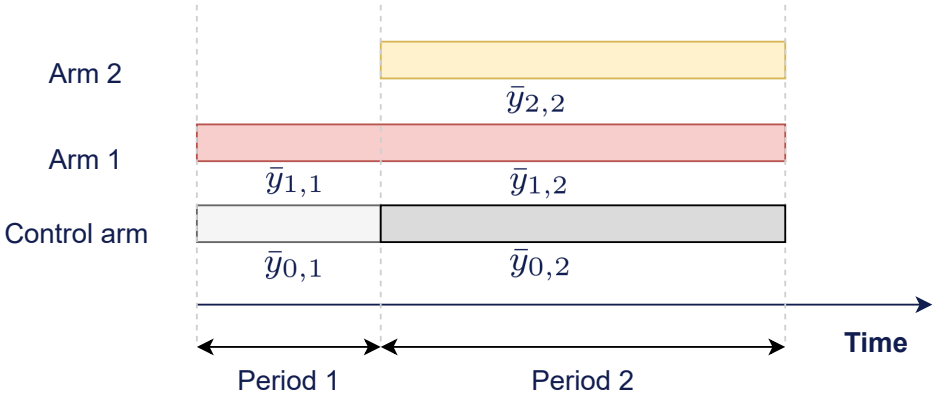

Treatment **effect estimator** using the model-based approach:

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

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

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

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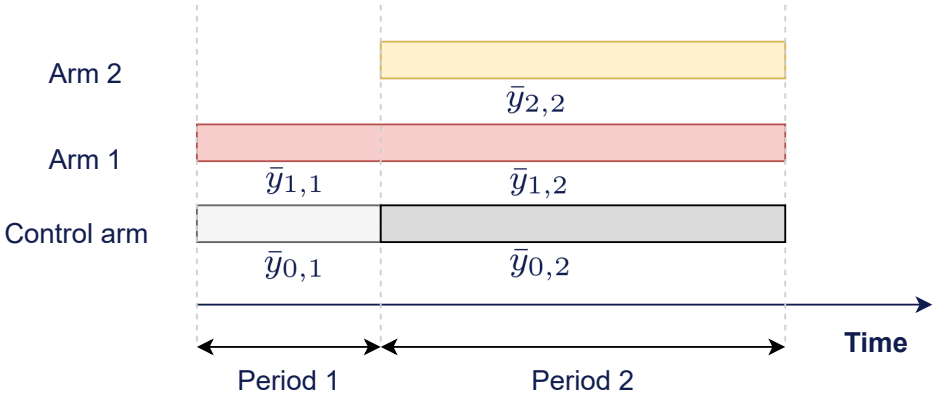

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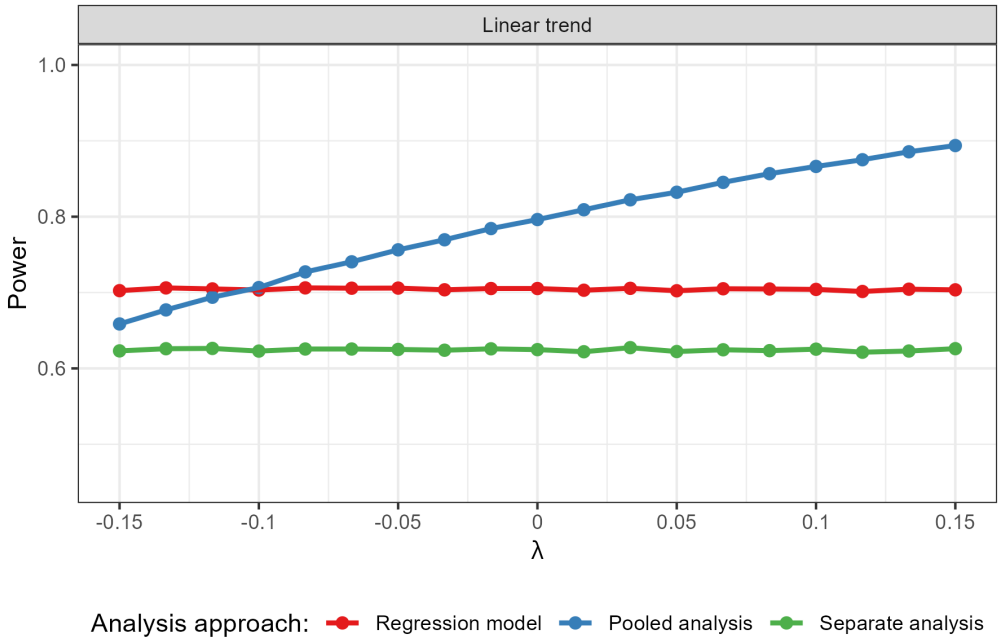
The effect estimator $\tilde{\theta}_2$ is **unbiased** if the time trends in all arms are equal and additive, regardless the functional form of the time trend.

Power in platform trials with equal time trends across arms

Simulation settings:

- Effect on treatment arm 2 (H_1)
- Same time trend for treatment and control arms (λ)
- Block randomization.

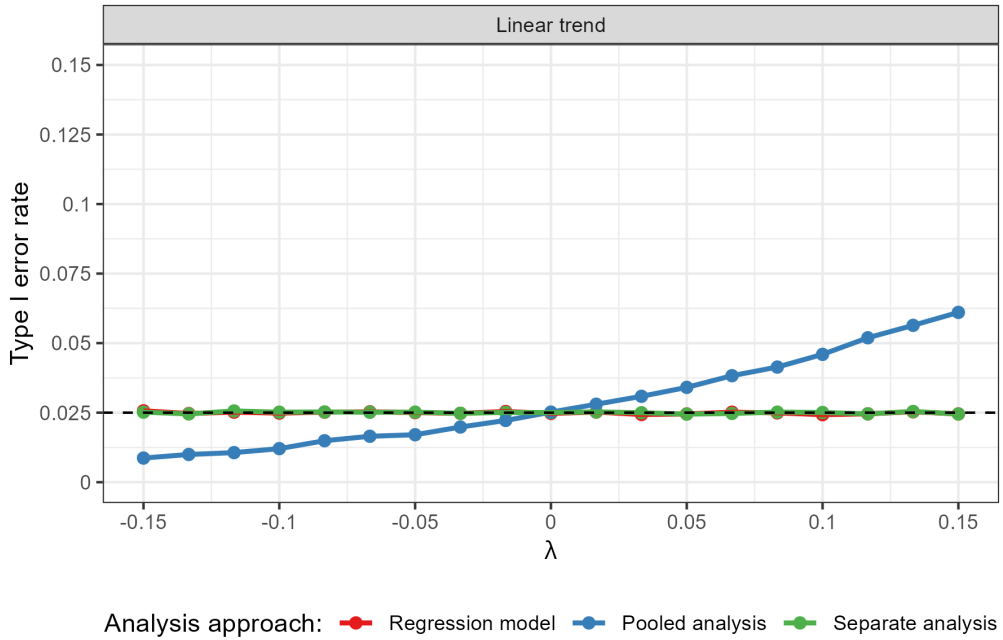


Model-based approach **improves the power** as compared to separate analysis using only CC.

Type 1 error in platform trials with equal time trends across arms

Simulation settings:

- No treatment effect on arm 2 (H_0)
- Same time trend for treatment and control arms (λ)
- Block randomization.



Model-based approach **controls the type I error** (T1E), even if the true trend is other than step-wise.

Key messages on the use of non-concurrent controls

- Non-concurrent controls may improve the trial's efficiency while decreasing the sample size but can introduce bias due to time trends if not adjusted for.
- When modeling the time trends the validity of the inferences relies on the assumption that
  - the time trends in all treatment arms are equal
  - the time trends are additive on the model scale
- Regulatory guidance for non-concurrent controls in platform trials are currently still limited.[7]

[7] Bofill Roig et al. (2023). On the use of non-concurrent controls in platform trials: A scoping review. Trials

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Can we further improve the efficiency of a trial using non-concurrent controls?

$\rightarrow$ **Optimal allocations**

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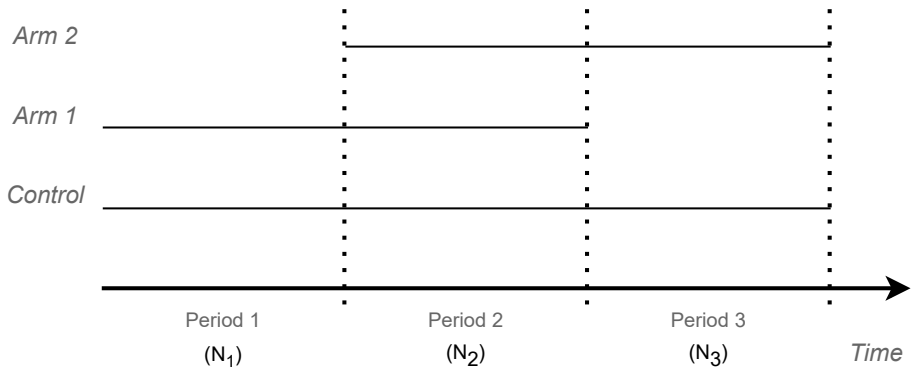
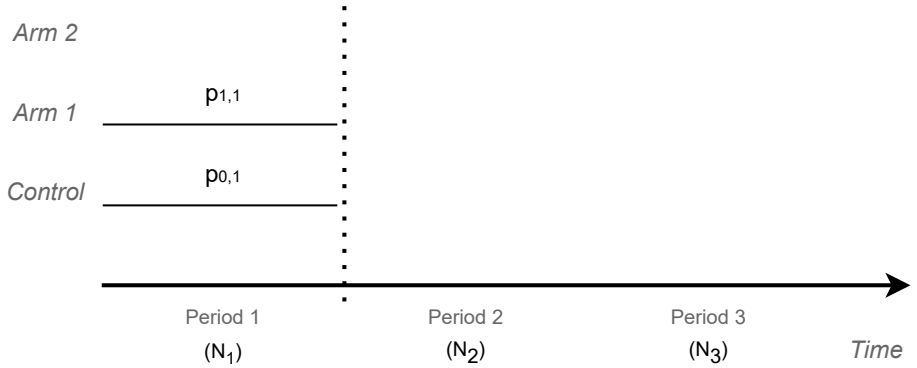
Optimal allocation in platform trials



- Arms i, **periods** s
- Sample sizes N and N_s
- Allocation rates per **arm and period**: $p_{i,s}$, $\sum_s p_{i,s} = 1$
- $X \sim \mathrm{N}(\mu_i, \sigma^2)$, σ known
- Effect sizes: $\theta_i = \mu_i - \mu_0$
- Null hypotheses $H_i : \theta_i \leq 0$

Optimal allocation in platform trials



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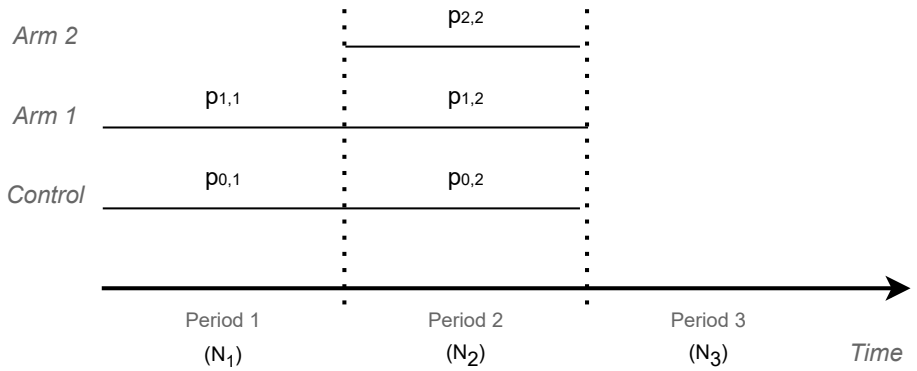

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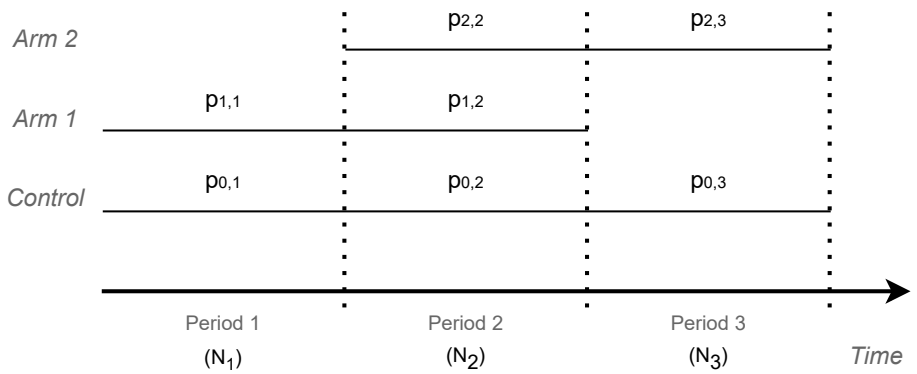

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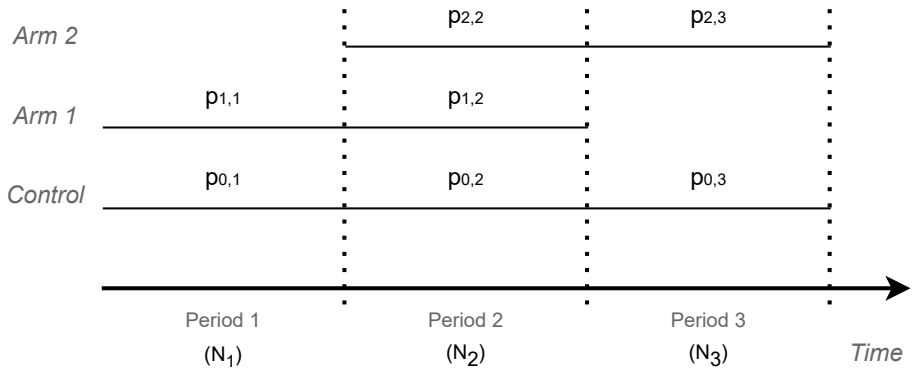

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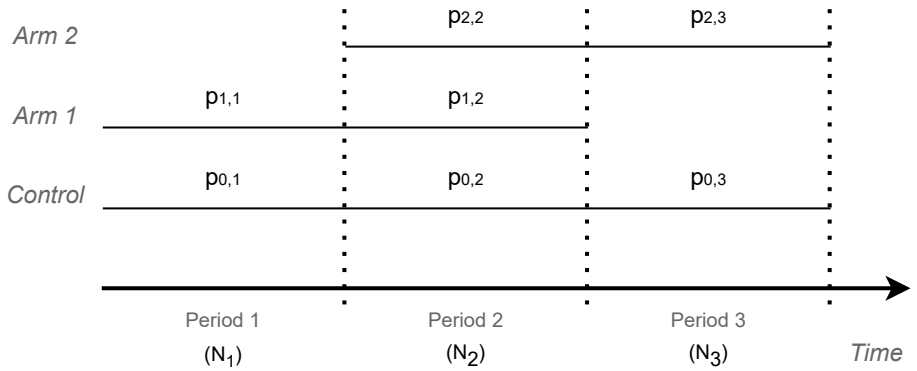
Estimators

- **Period stratified estimators** $\hat{\theta}_1$ using only concurrent controls.
- **Period stratified estimators** $\tilde{\theta}_2$ using non-concurrent controls based on model adjustments.

Optimal allocation in platform trials



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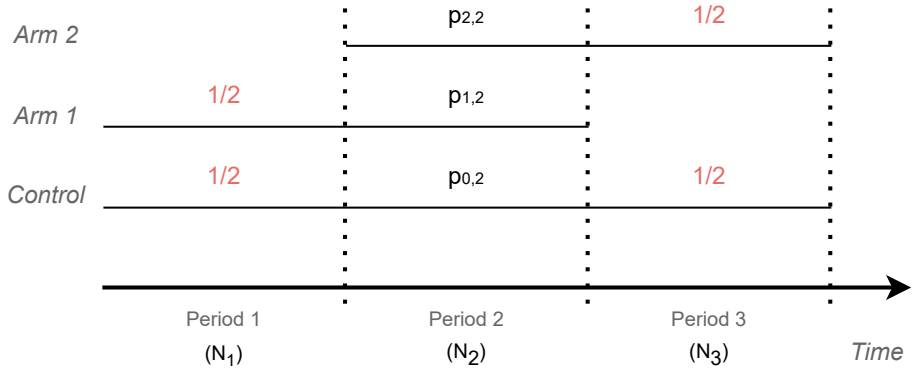
Objective: To minimise

$$\max(\mathrm{Var}(\hat{\theta}_1), \mathrm{Var}(\tilde{\theta}_2))$$

by means of optimising $\boldsymbol{p_{i,s}}$

Optimal allocations with and without using non-concurrent controls

Fix N, N_1, N_2 and optimise $p_{i,s}$
The solution leads to equal allocations in periods 1 and 3.



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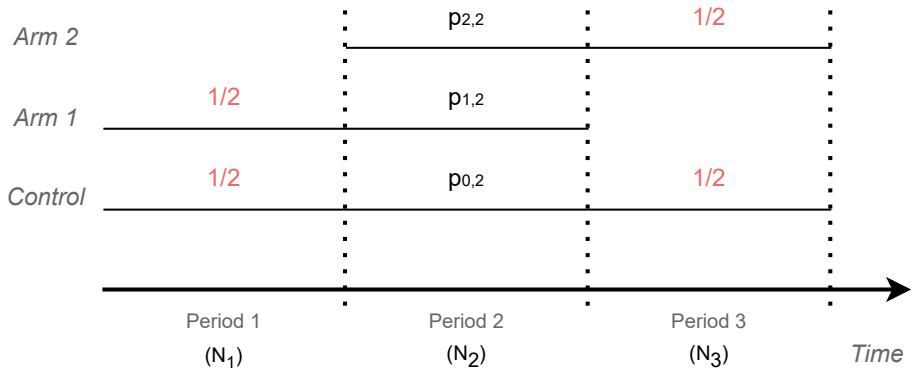

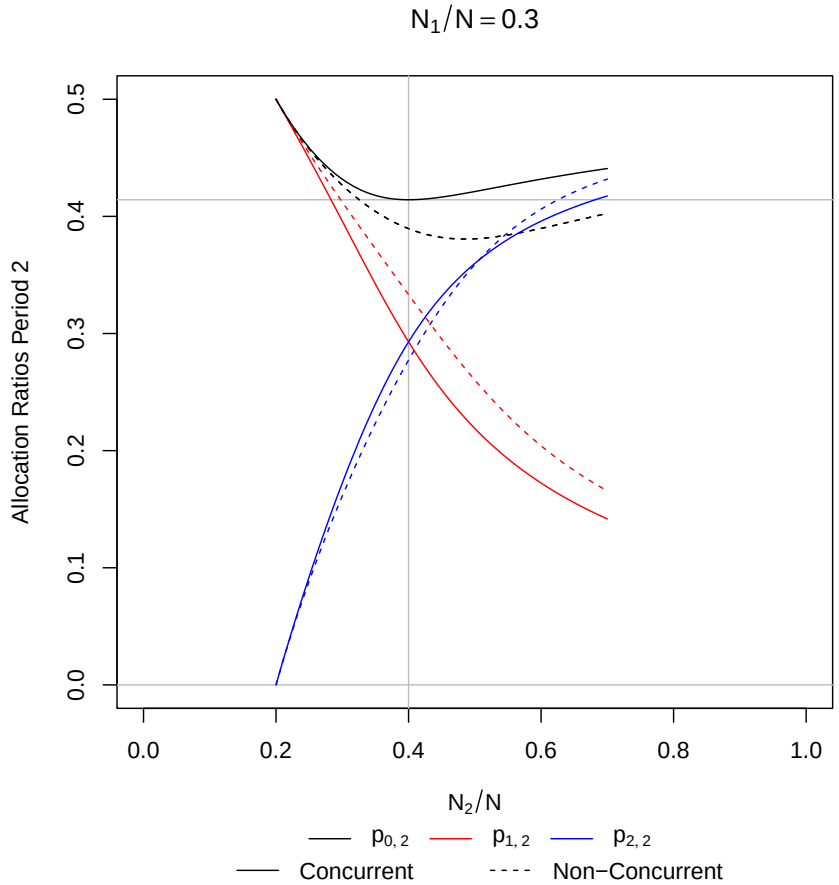

- The proportion of patients allocated to control in period 2, $p_{0,2}$, is lower when non-concurrent controls are used.
- The proportion $p_{0,2}$ may be lower than the proportion of patients assigned to arm 1 or 2, $p_{1,2}$ and $p_{2,2}$.

Conclusions on optimal allocations

- The multi-armed trial (where all treatment arms enter at the start) is more efficient than platform trials with staggered entry of treatments, even when utilising non-concurrent controls.
- If treatments enter at later time points, the optimal allocation depends on the given entry times and all treatments continue to the very end of the platform trial to maximise the sharing of controls.
- If the entry time of Arm 2 is unknown, equal allocation will remain in the first period and the optimal allocation ratios for period 2 can be computed when Arm 2 enters the platform assuming the exit time of Arm 1 fixed.

References

1. 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. (2022). On model-based time trend adjustments in platform trials with non-concurrent controls. BMC Medical Research Methodology.
2. Krotka, P., Hees, K., Jacko, P., Magirr, D., Posch, M., & Bofill Roig, M. (2023). NCC: An R-package for analysis and simulation of platform trials with non-concurrent controls. Accepted in SoftwareX. Preprint arXiv:2302.12634
3. Saville, B. R., Berry, D. A., Berry, N. S., Viele, K., & Berry, S. M. (2022). The Bayesian Time Machine: Accounting for temporal drift in multi-arm platform trials. Clinical Trials.
4. Marschner, I. C., & Schou, I. M. (2022). Analysis of adaptive platform trials using a network approach. Clinical Trials.
5. Lee, K. M., & Wason, J. (2020). Including non-concurrent control patients in the analysis of platform trials: is it worth it? BMC Medical Research Methodology.
6. Bofill Roig, M., Glimm, E., Mielke, T., & Posch, M. (2023). Optimal allocation strategies in platform trials. arXiv:2304.03035 [stat.ME]
7. Bennett, M., & Mander, A. P. (2020). Designs for adding a treatment arm to an ongoing clinical trial. Trials.

Thank you for your attention!

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