Optimal allocation strategies for platform trials

Marta Bofill Roig, Ekkehard Glimm, Tobias Mielke and Martin Posch

Adaptive Designs and Multiple Testing Procedures Workshop 2023

MEDICAL UNIVERSITY
OF VIENNA

Acknowledgements

WP2 of Scientific, Regulatory and Operational Methodology

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arXiv:2304.03035 [stat.ME]

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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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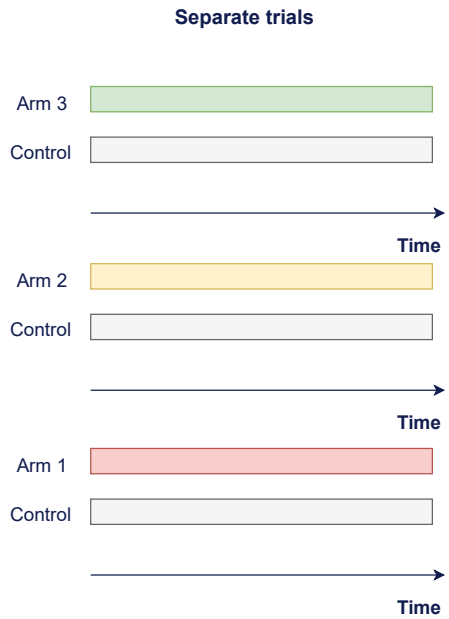

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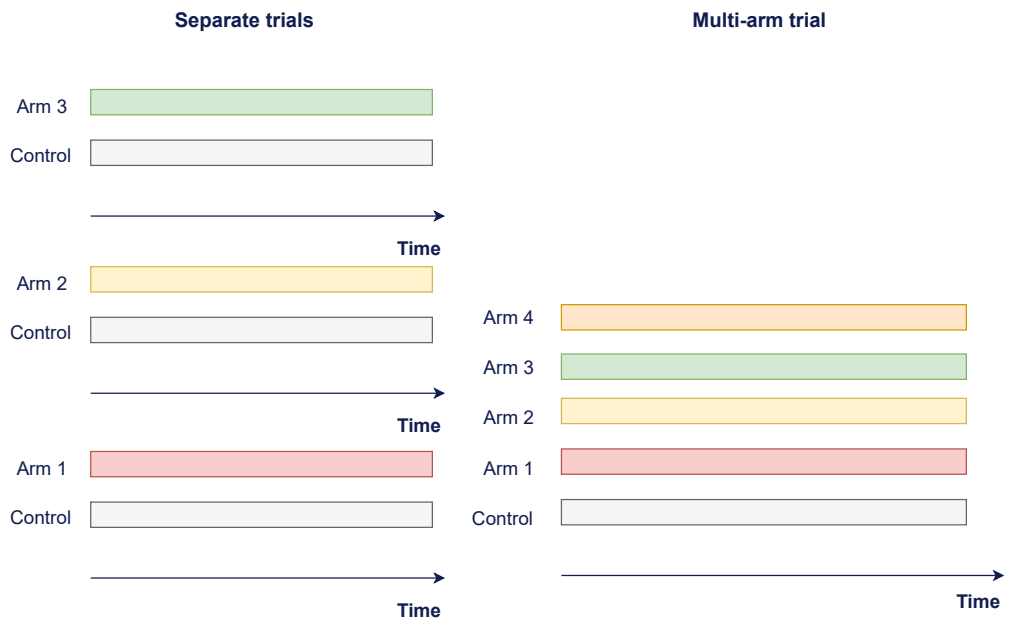

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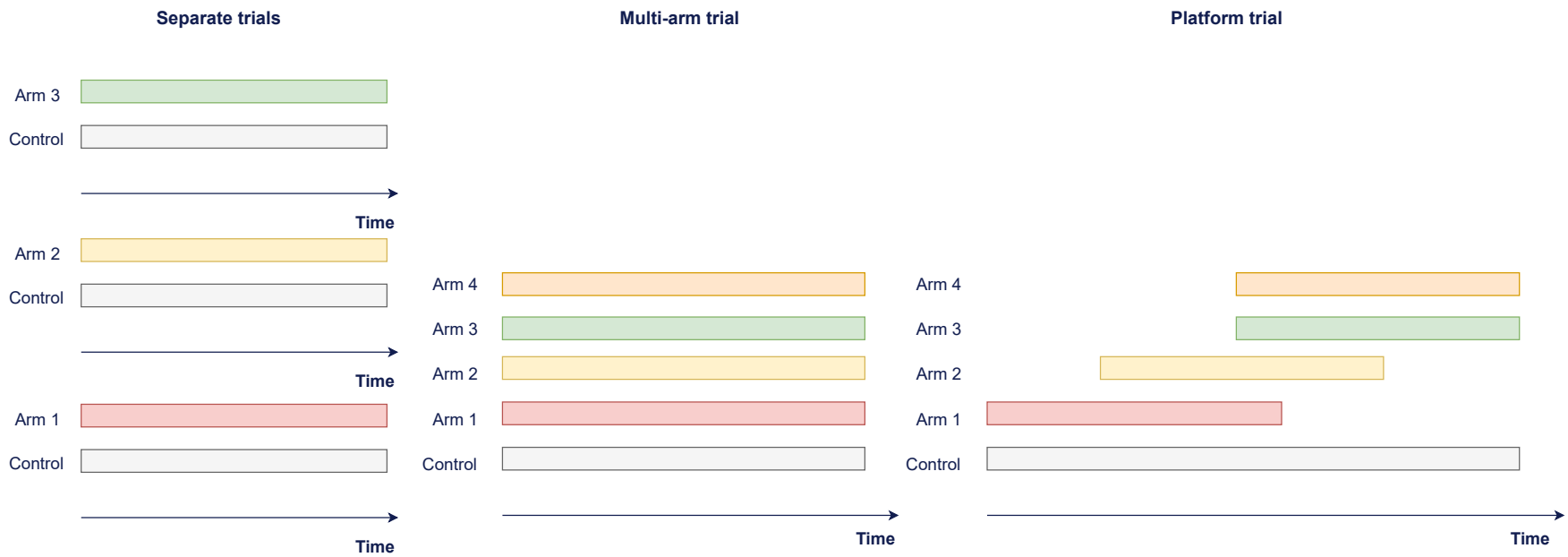

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Optimal allocation of patients to treatment and control arms

In multi-arm trials with a shared control, further efficiency gains can be obtained by optimising the allocation rates of participants to the different treatment groups.

Optimal rates depend on the **optimisation criteria** and **analysis method**.

In platform trials,

- Optimal allocations to maximize the probability to find all treatments that are better than control.[2]
- Optimal allocations to minimize the total sample size to achieve a desirable marginal power level.[3]

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Optimal allocations for trials considering time-adjusted analyses, and using concurrent data only or concurrent and non-concurrent data.

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Optimal allocation in multi-arm trials

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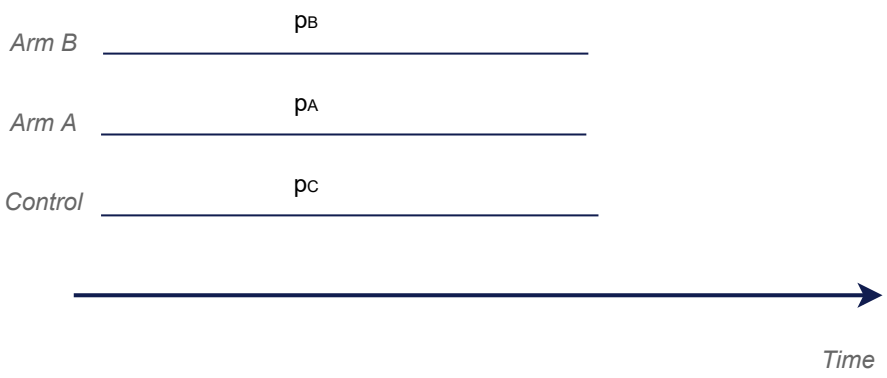
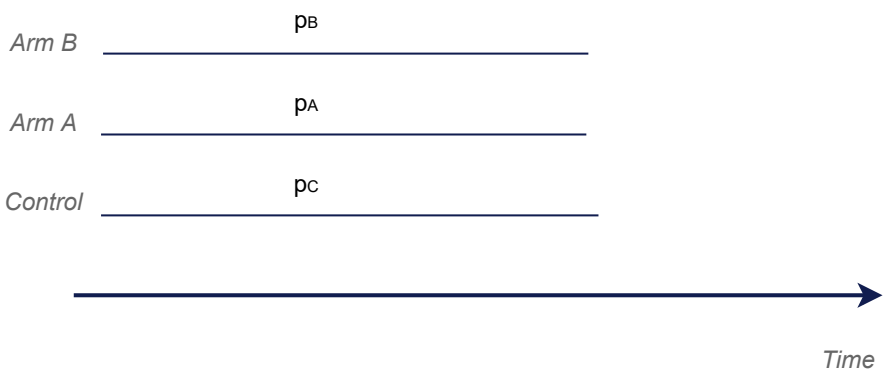


- Arms $i = C, A, B$
- Total sample size N
- Allocation probability per arm: p_i
- $X \sim \mathrm{N}(\mu_i, \sigma^2)$, σ known
- Effect sizes: $\theta_i = \mu_i - \mu_c$
- Null hypotheses $H_i : \theta_i \leq 0$
- Estimators $\hat{\theta}_i$

Optimal allocation in multi-arm trials



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by means of optimising p_i

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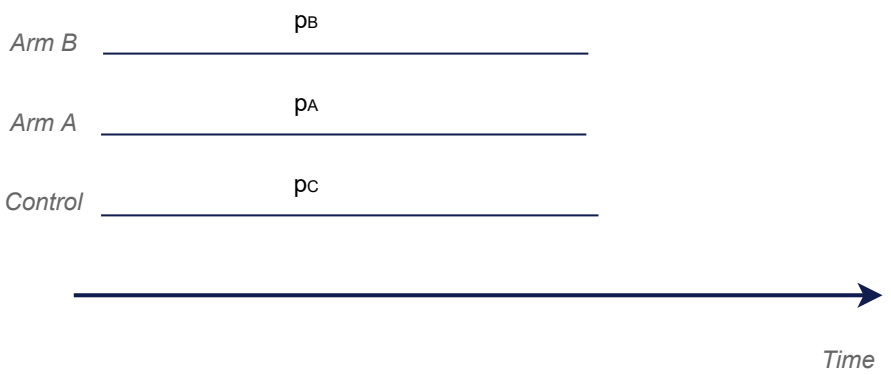

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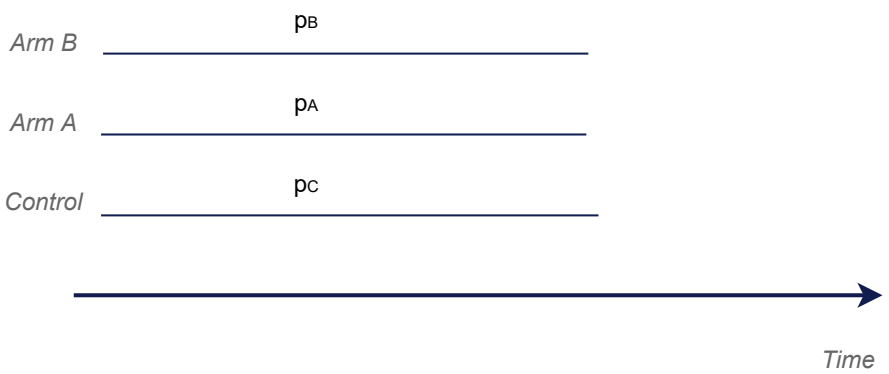
In multi-arm trials with k treatment arms, the optimal allocation rates are

$$p_A = p_B \quad \text{and} \quad p_C/p_A = \sqrt{k}$$

and then variances are equal. If $k = 2$

$$p_A = p_B = \frac{\mathbf{1}}{2+\sqrt{2}} \quad \text{and} \quad p_C = \frac{\mathbf{\sqrt{2}}}{2+\sqrt{2}}$$

Optimal allocation in multi-arm trials



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In multi-arm trials with k treatment arms, the optimal allocation rates are

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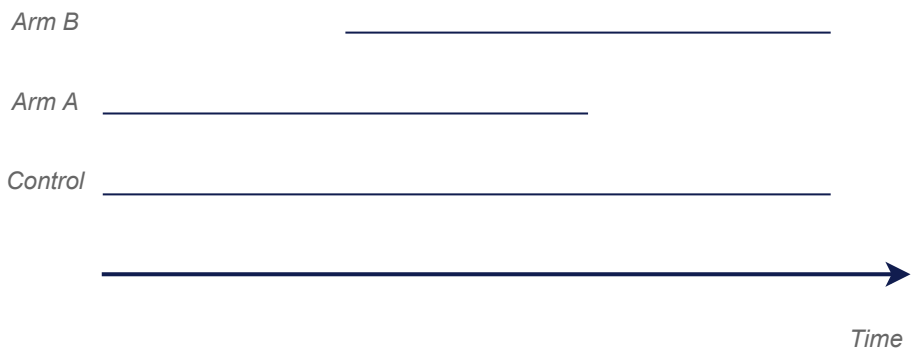
But, are these rates also optimal in platform trials?

Optimal allocation in platform trials



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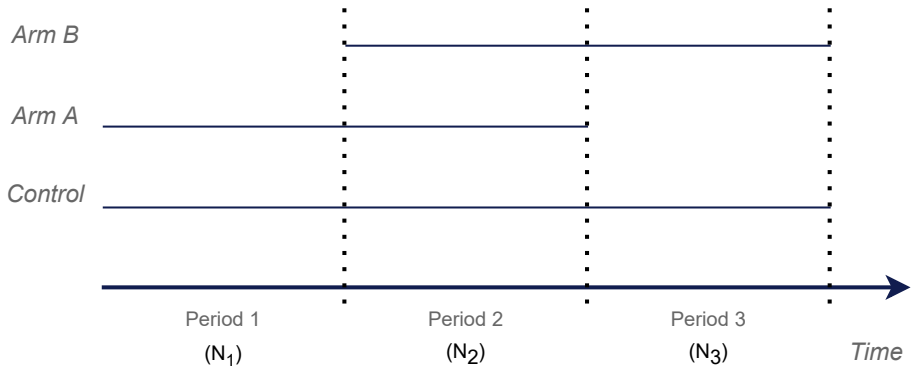

- Arms i, **periods** s
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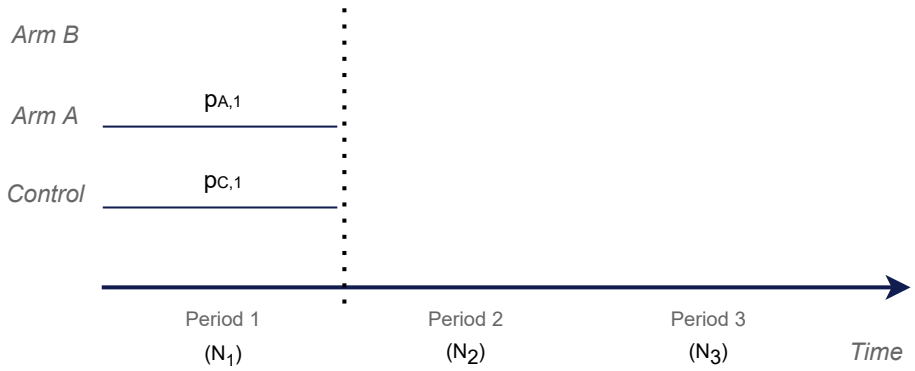

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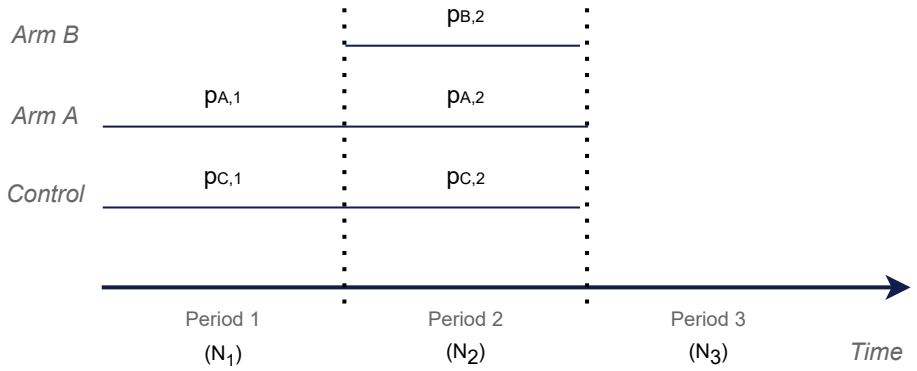

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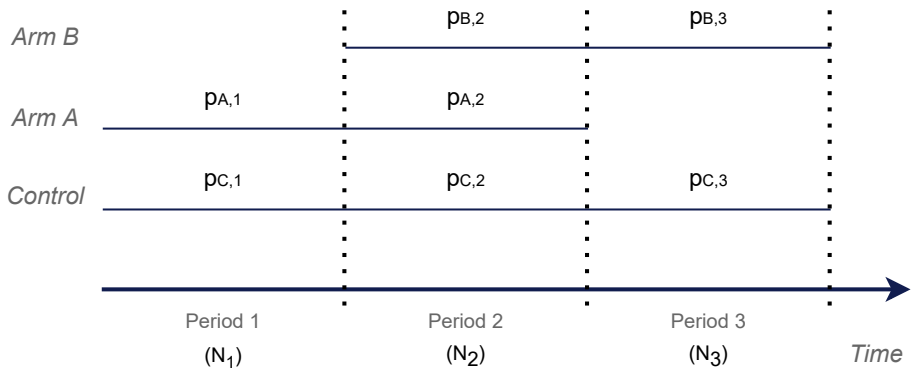

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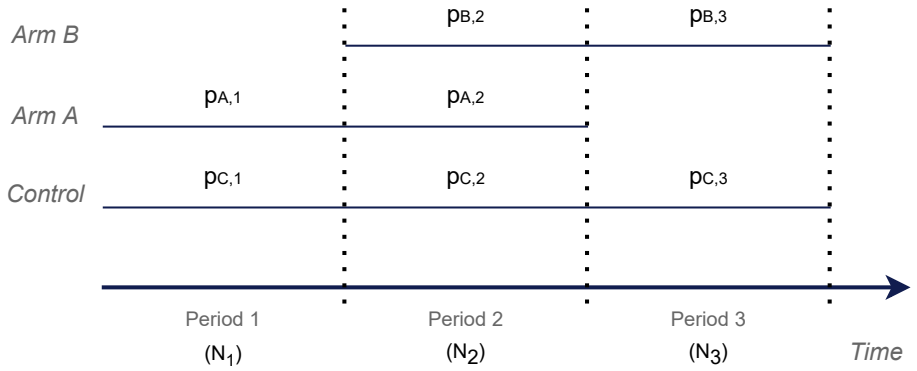

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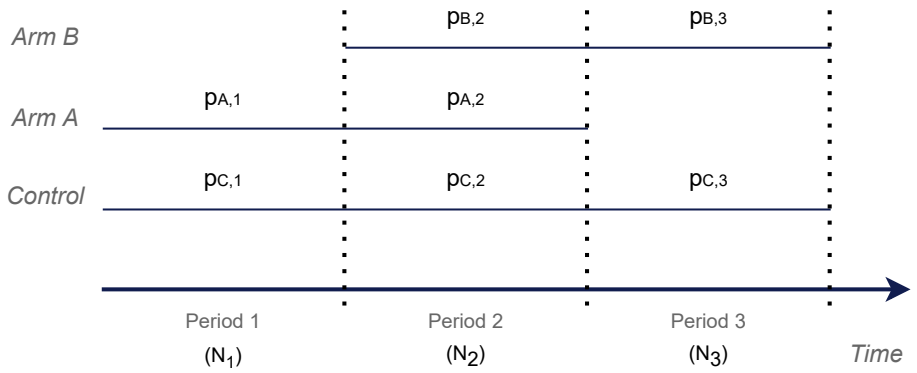

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Optimal allocations depend on the **trial design configuration** with respect to the sample sizes per period.

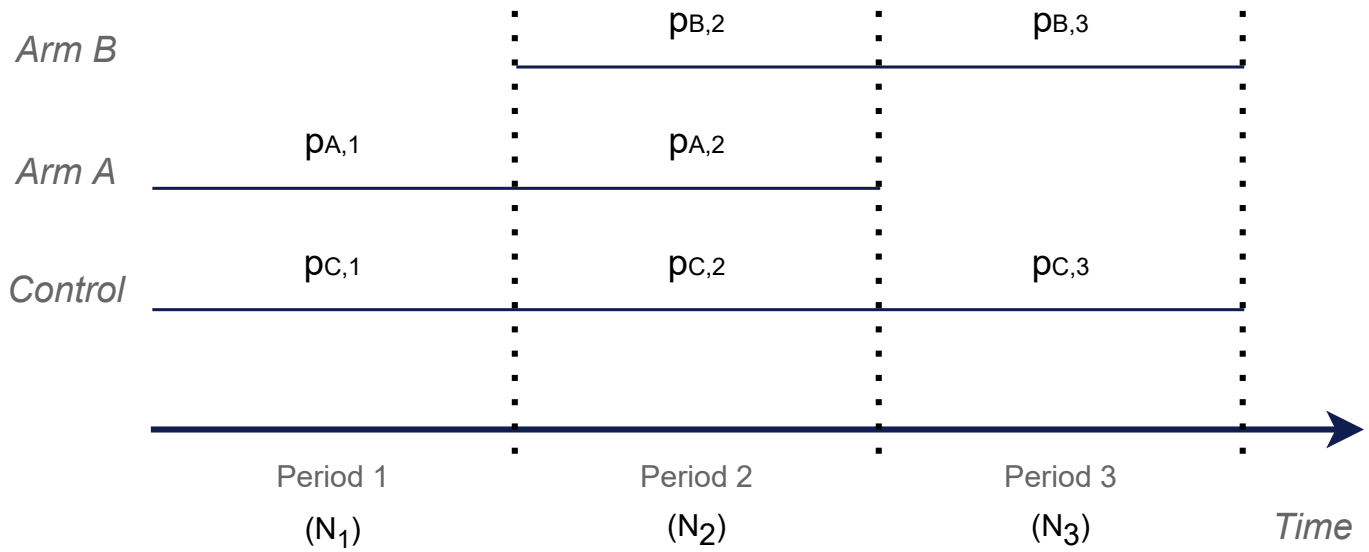
Also, under suitable conditions, the solution satisfies

- $Var(\hat{\theta}_A) = Var(\hat{\theta}_B)$

Optimal allocations

For given entry time of Arm B and exit time of Arm A

Assume N, N_1, N_2 (and N_3) are fixed and optimise $p_{i,s}$



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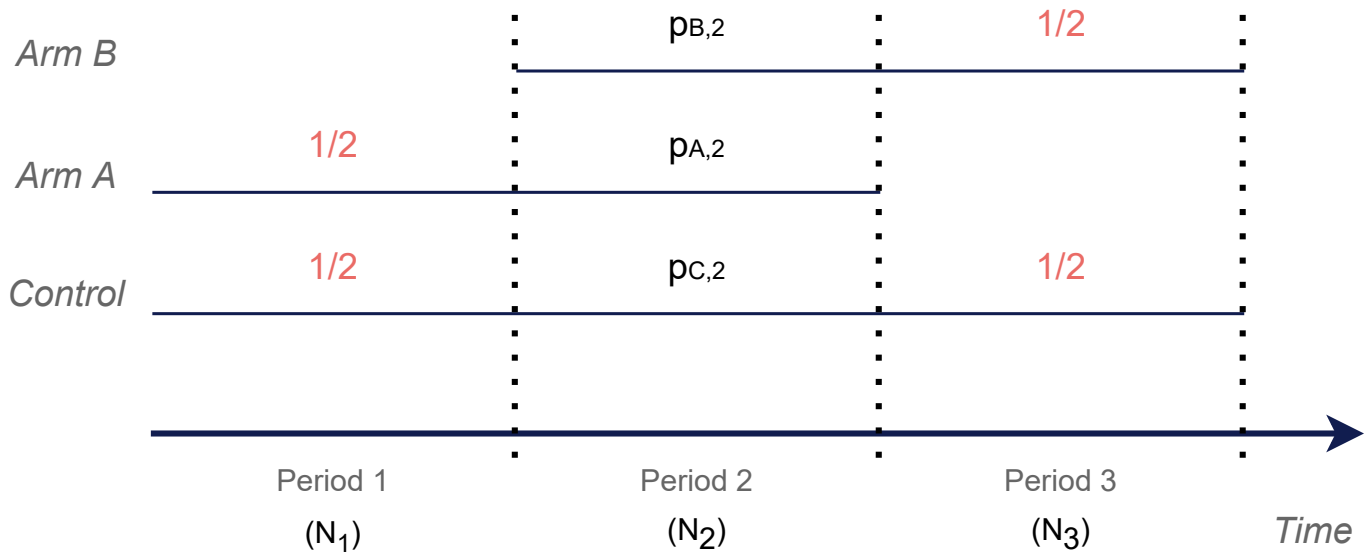

Optimal allocations:

- Equal allocation between treatment and control arms in **periods 1 and 3**.
- No closed form solution for the optimal rates in **period 2**.
- Optimal rates in period 2 depend on N_1 and N_2.

Optimal allocation in period 2 for a trial with fixed N, N_1 and N_2

- The proportion of patients allocated to control in period 2, $p_{C,2}$, is greater or equal than $p_{A,2}$ and $p_{B,2}$.
- The proportion $p_{C,2}$ is not monotone in N_2, and it takes the minimum when $N_1 = N_3$.
- If $N_1 = N_3$, then

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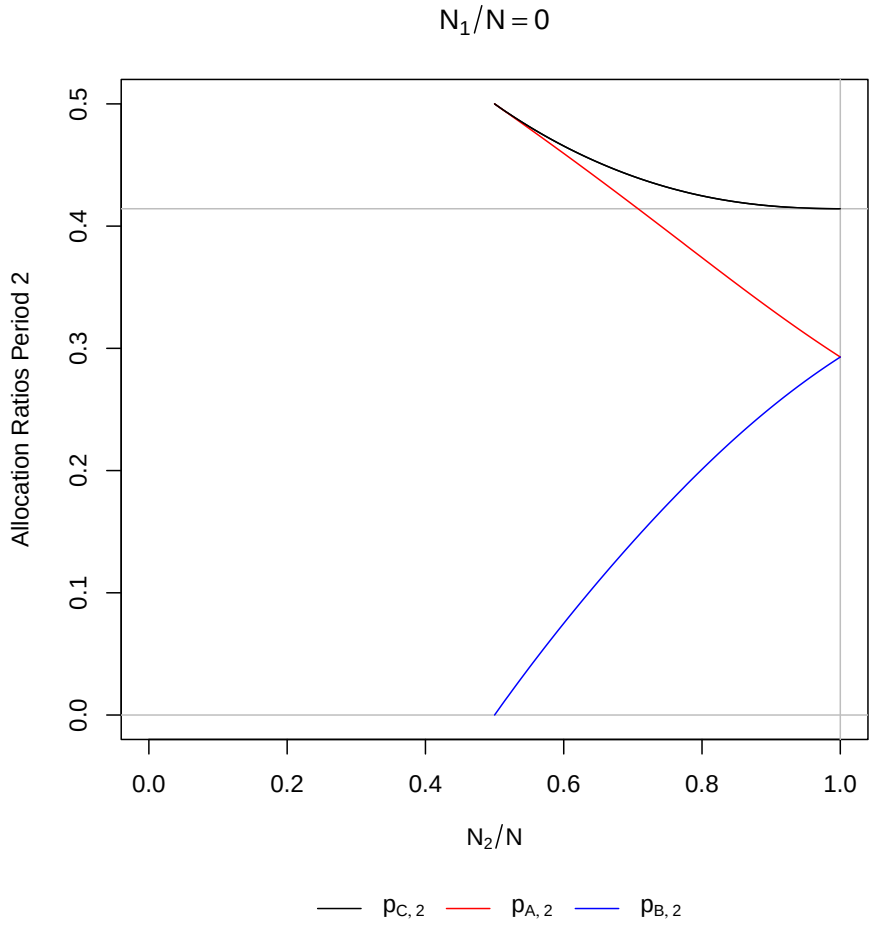

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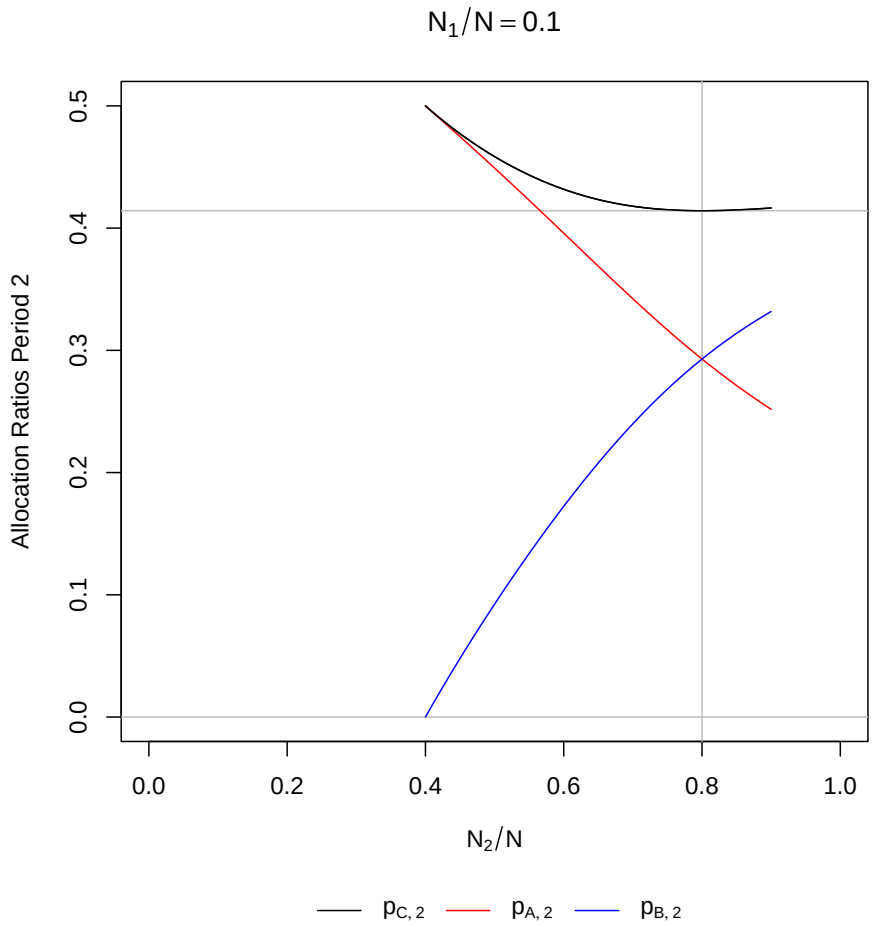

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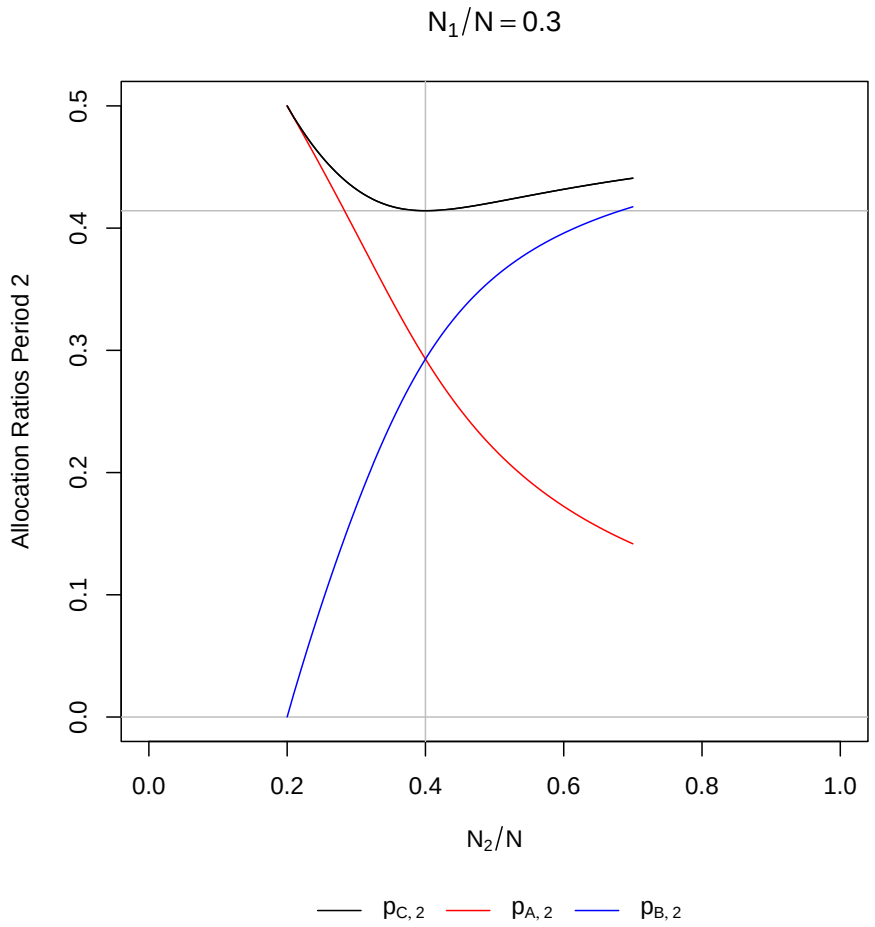

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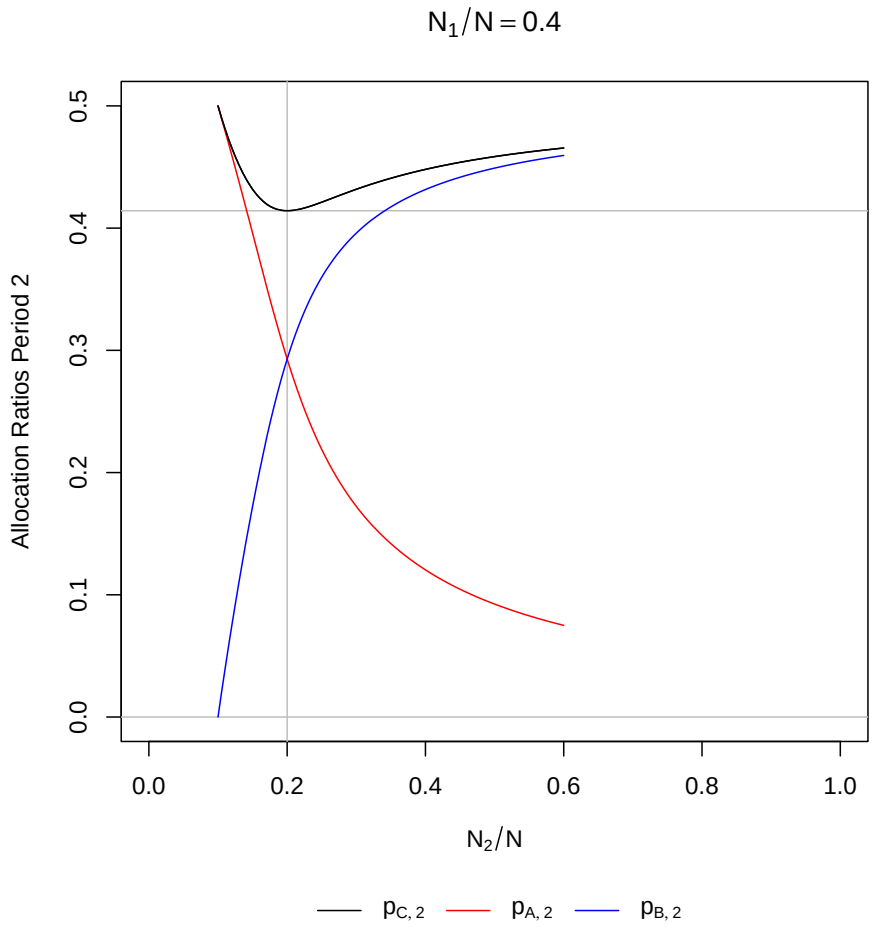

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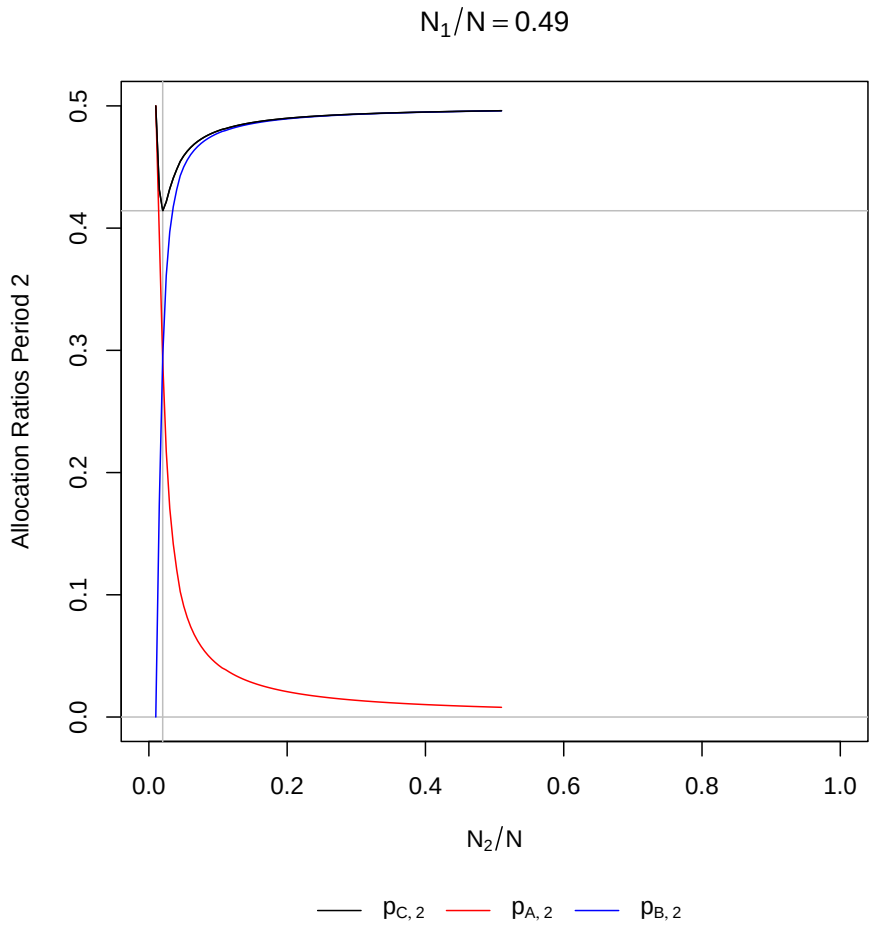
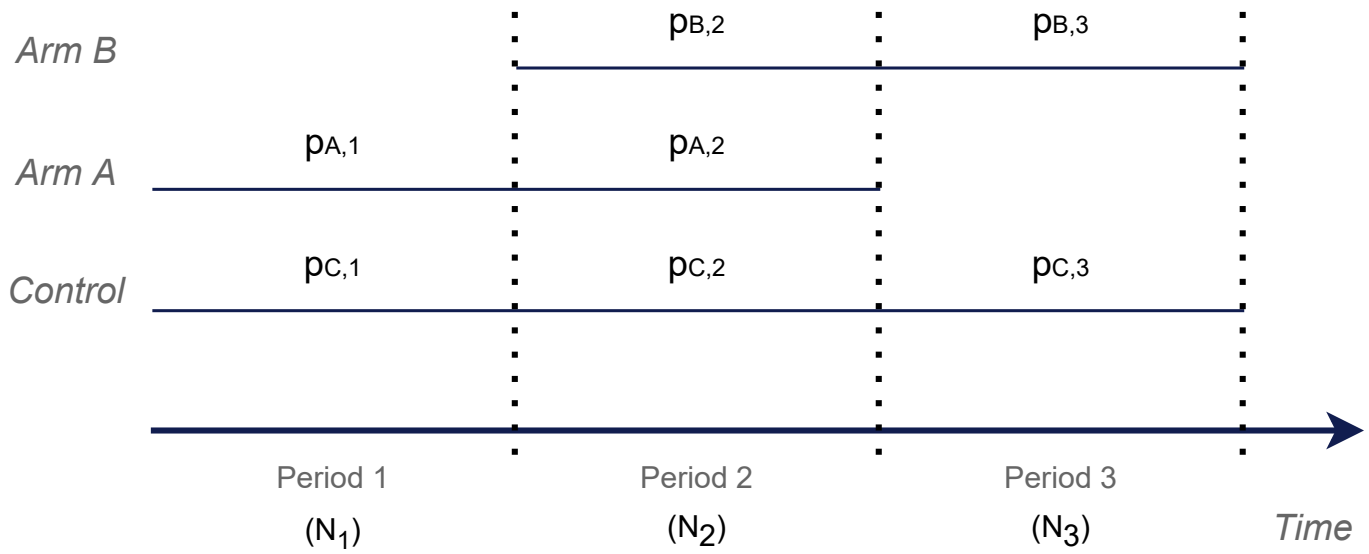


Optimal allocations depending on the trial design

What if in addition optimise N_2?

Fix N and N_1 and optimise $p_{i,s}$ and N_2, N_3



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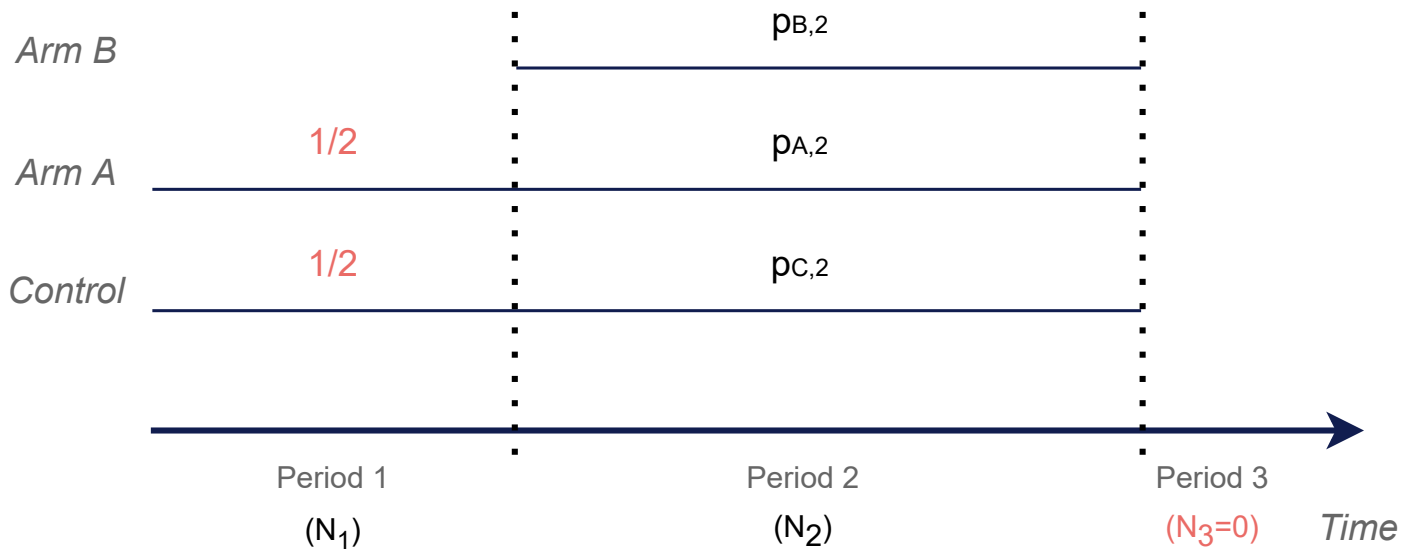


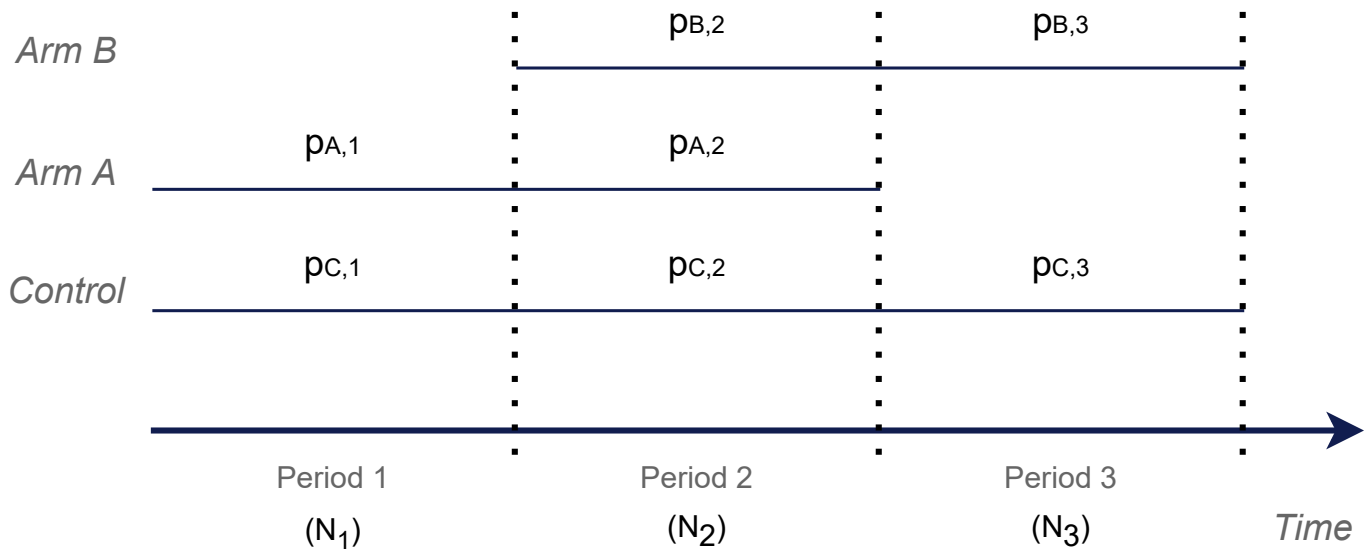
Optimal allocations:

- The solution leads to $N_3 = 0$ and thus a **two-period trial**.
- The design is a particular case of the previous where $N_2 = N - N_1$.

Optimal allocations depending on the trial design

With no restrictions on entry and exit times

Fix N and optimise $p_{i,s}$ and the period sample sizes N_1,N_2,N_3



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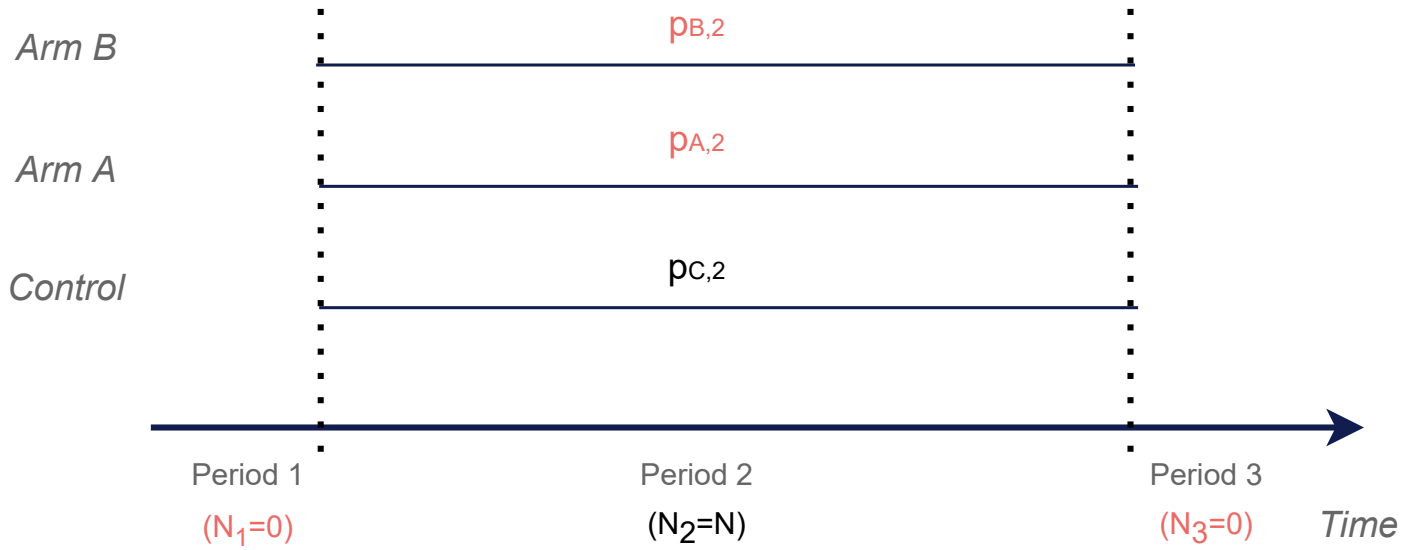
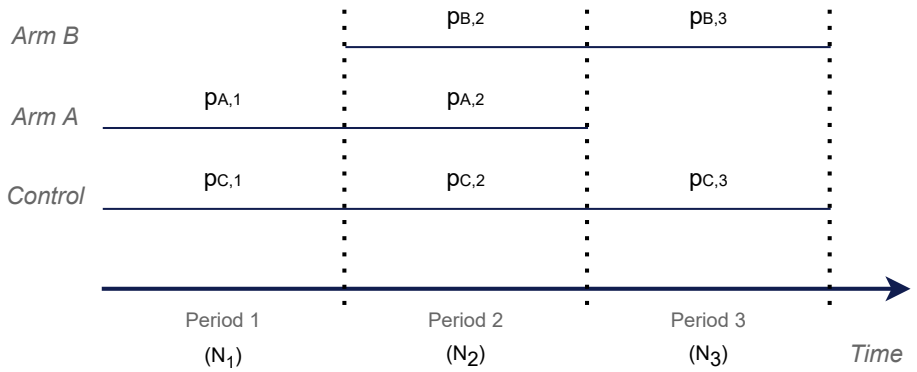


Optimal allocations:

- The solution leads to $N_1 = N_3 = 0$ and thus a **classical multi-arm trial**.
- The optimal solution is $p_{A,2} = p_{B,2}$ and $p_{C,2}/p_{A,2} = \sqrt{2}$.

What about optimal rates if non-concurrent controls are used?



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[4] 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.

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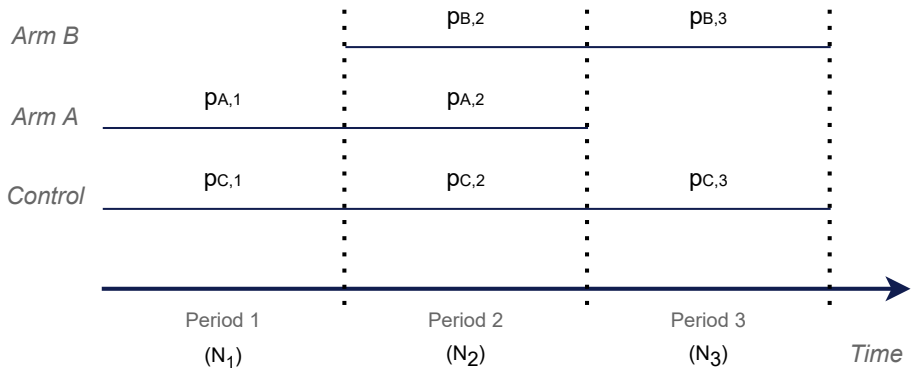

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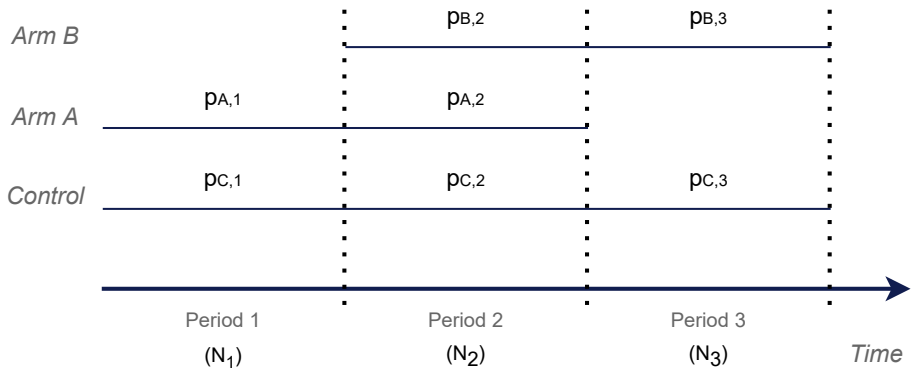
- Effect sizes: $\theta_i = \mu_i - \mu_c$
- Null hypotheses $H_i : \theta_i \leq 0$

Estimators

- **Period stratified estimators** $\hat{\theta}_A$ using only concurrent controls.
- **Period stratified estimators** $\tilde{\theta}_B$ using non-concurrent controls based on model adjustments.[4]

[4] 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.

What about optimal rates if non-concurrent controls are used?



- Arms i, **periods** s
- Sample sizes N and N_s
- Allocation rates per **arm and period**: $p_{i,s}$
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Estimators

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Objective: To minimise

$$\max(\mathrm{Var}(\hat{\theta}_A), \mathrm{Var}(\tilde{\theta}_B))$$

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

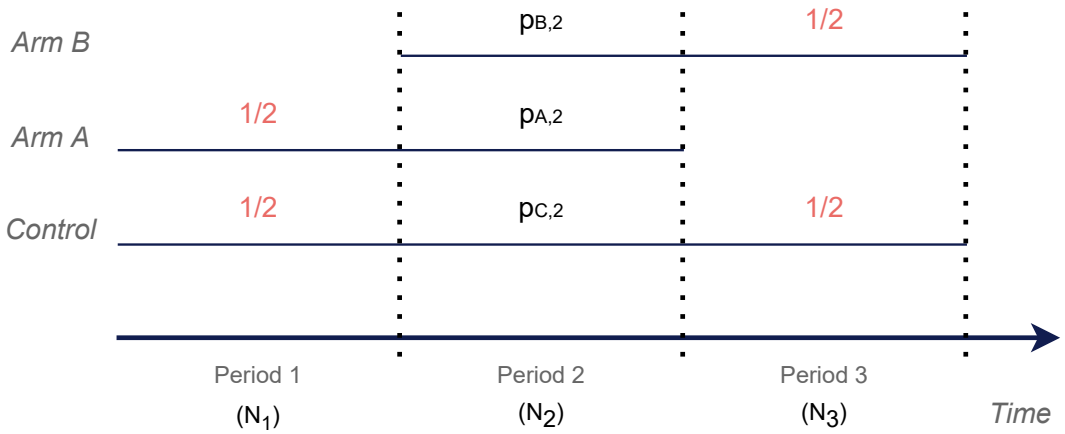
Under suitable conditions, the solution satisfies $Var(\hat{\theta}_A) = Var(\tilde{\theta}_B)$.

[4] 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.

Optimal allocations for trials with non-concurrent controls

Design 1: Fix N, N_1, N_2 (and N_3) and optimise $p_{i,s}$

- The solution leads to equal allocations in periods 1 and 3.
- Closed form solution for the optimal rates in period 2.



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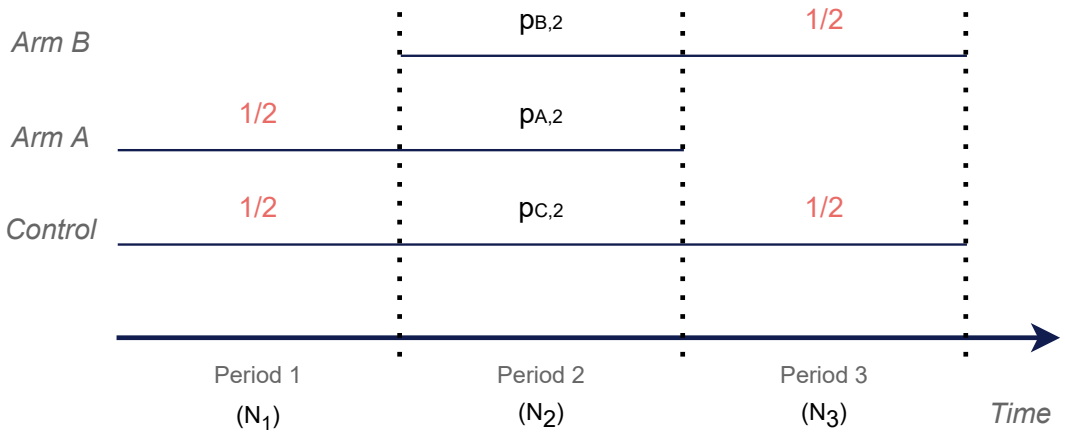

Design 2: Fix N and N_1 and optimise $p_{i,s}$ and the sample sizes N_2,N_3

- The solution is a two-period trial with equal allocation in period 1.
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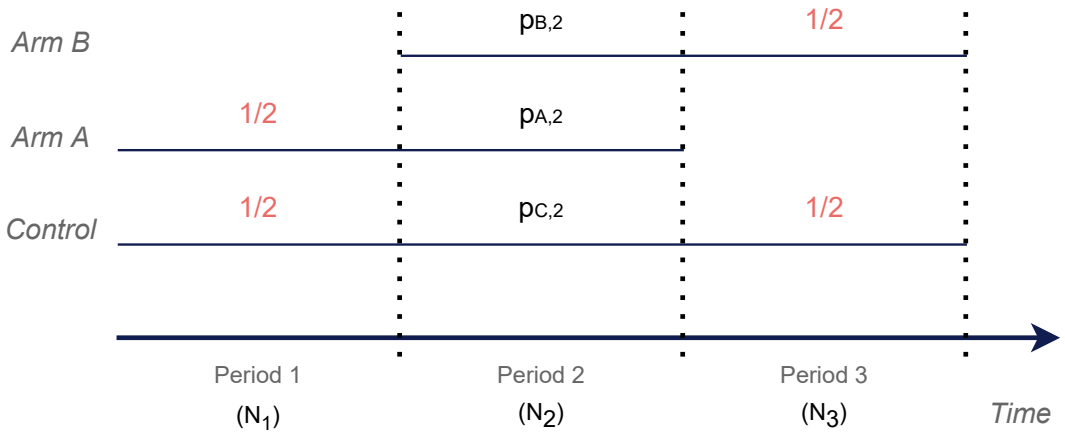

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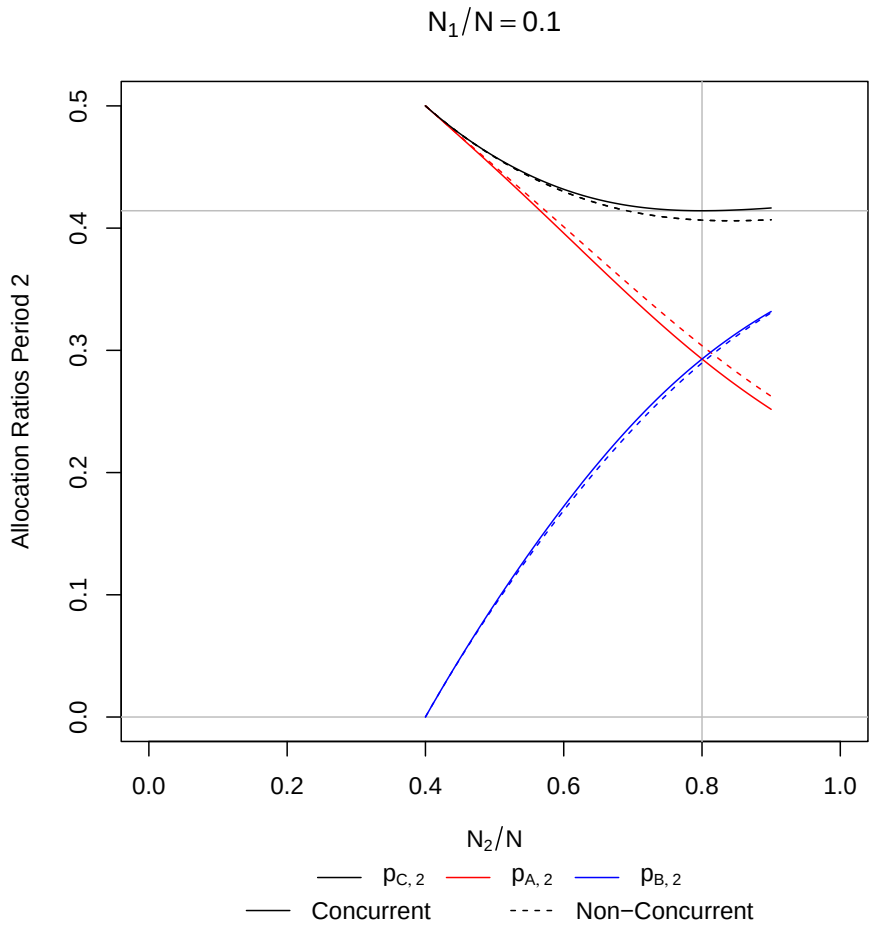
Design 3: Fix N and optimise $p_{i,s}$ and the period sample sizes N_1,N_2,N_3

- The optimal solution is a multi-arm trial with $p_{A,2} = p_{B,2}$ and $p_{C,2}/p_{A,2} = \sqrt{2}$.

Optimal allocations with and without using non-concurrent controls

- The pattern of the optimal allocation rates is similar to the trial with concurrent controls.
- The proportion of patients allocated to control in period 2, $p_{C,2}$, is lower when non-concurrent controls are used.
- The proportion $p_{C,2}$ may be lower than the proportion of patients assigned to arm 1 or 2, $p_{A,2}$ and $p_{B,2}$.



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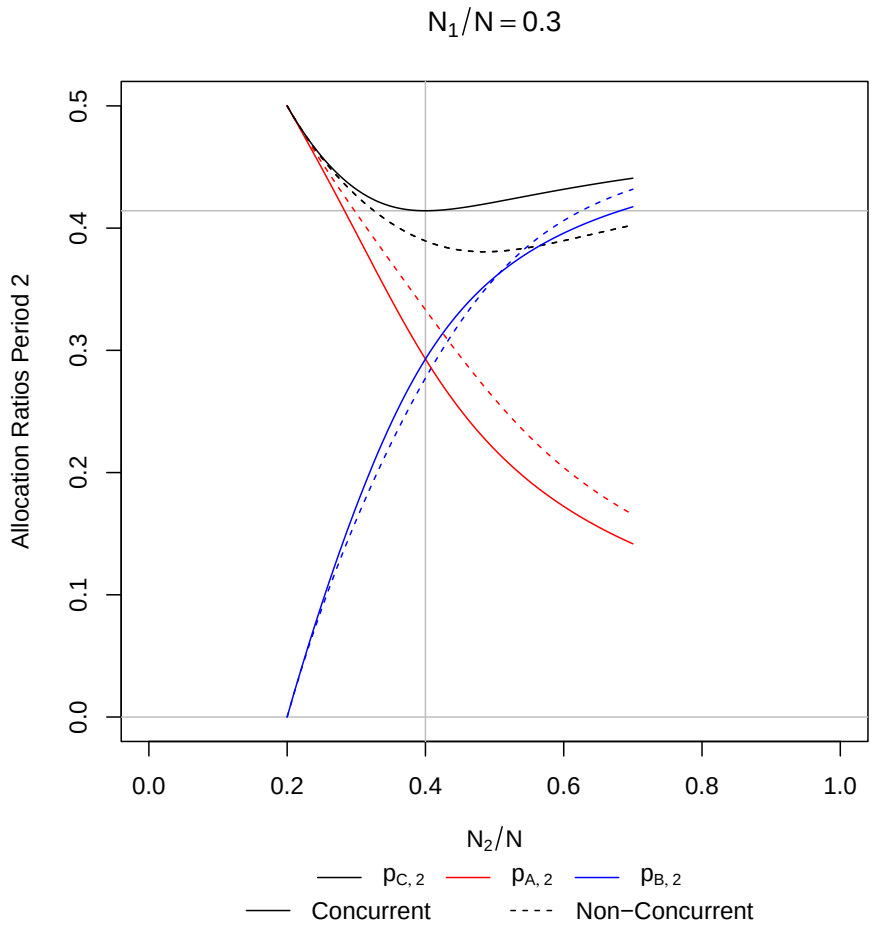

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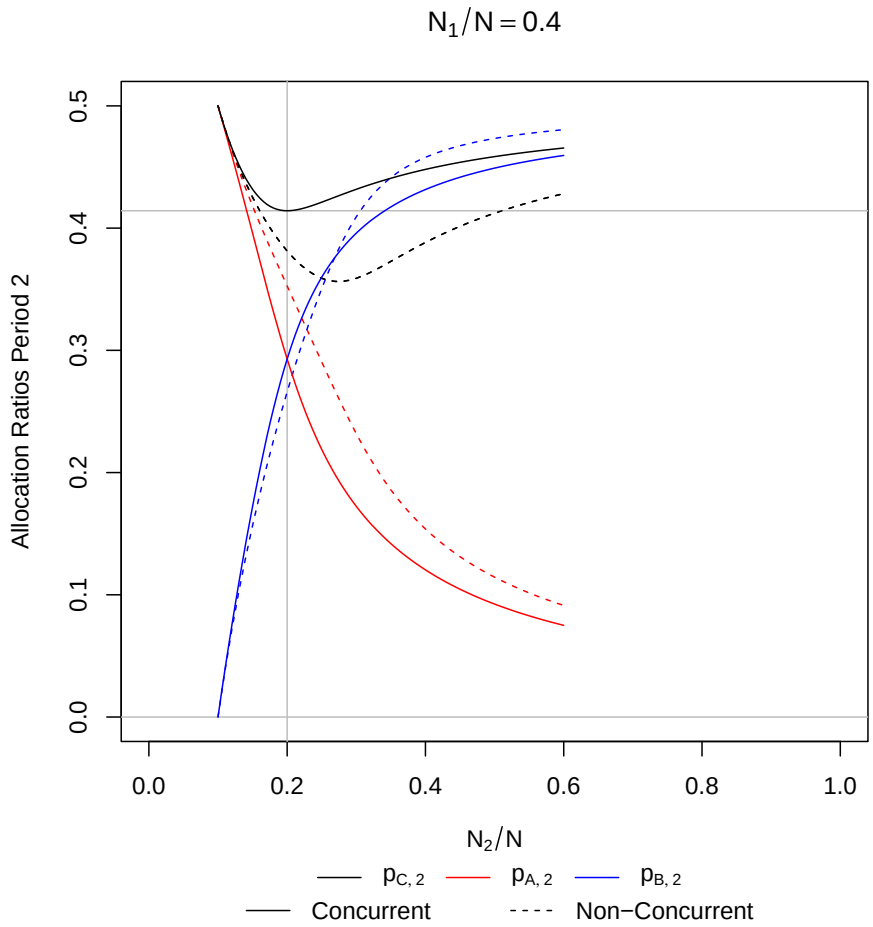

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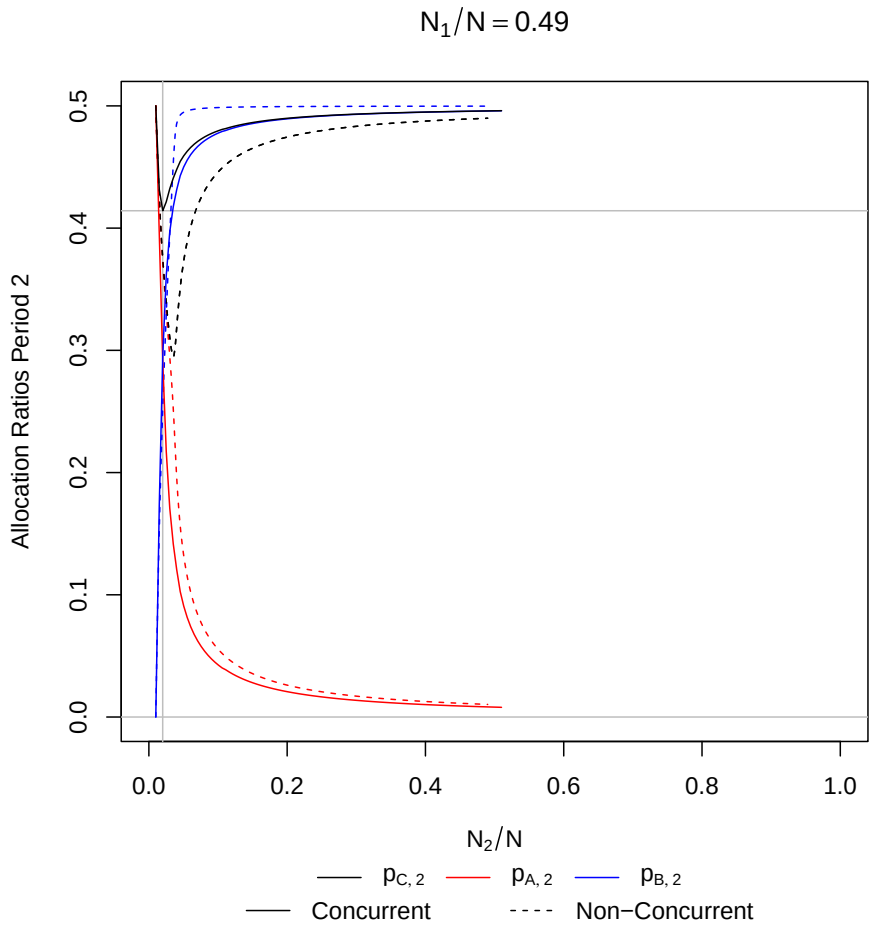
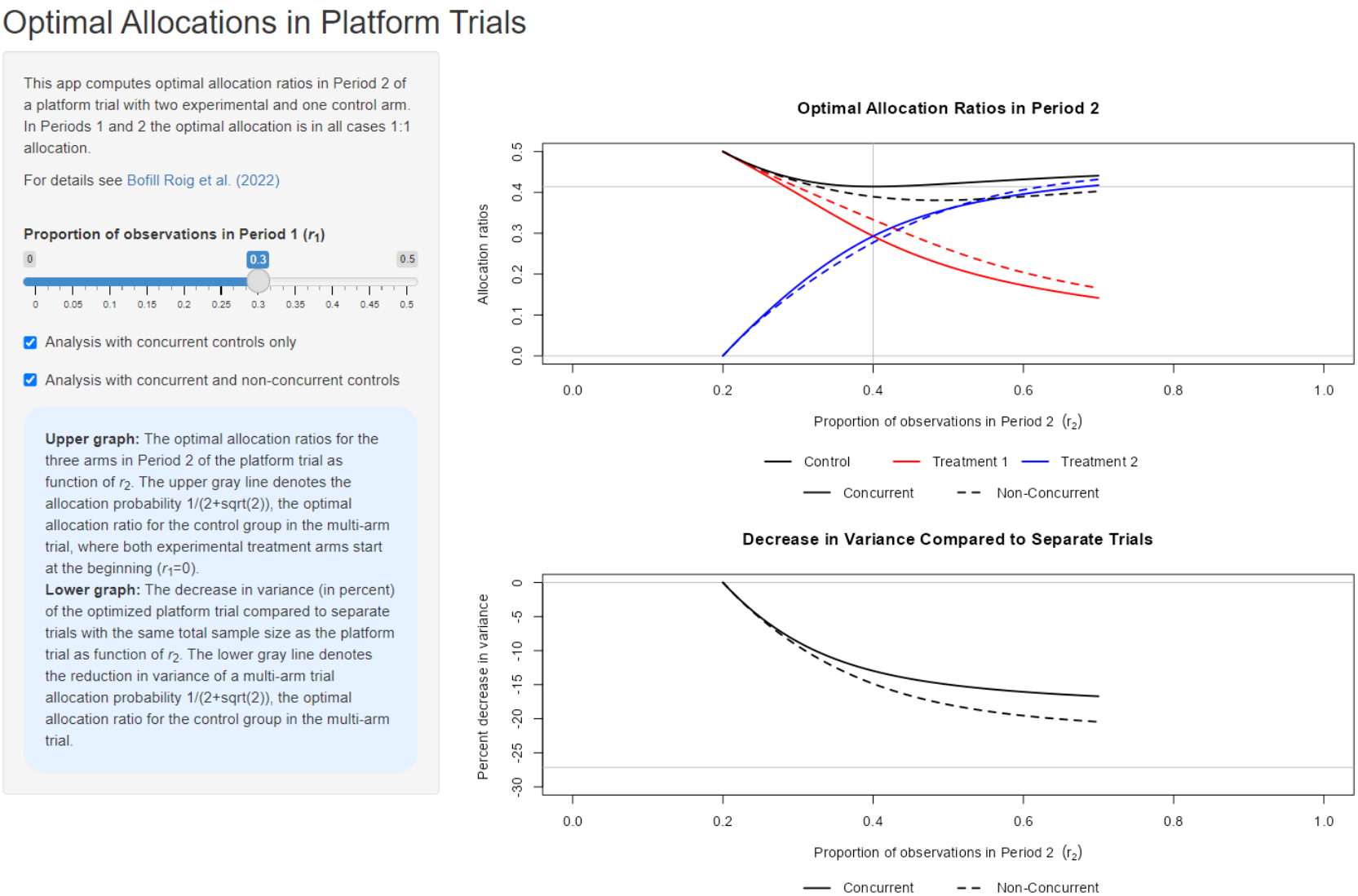


Decrease in variance when using the optimal allocations

- Shiny app available at: `https://github.com/MartaBofillRoig/Allocation`



Conclusions

- 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.
- In practice, the time a treatment is in the platform should be restricted and, for this case, a restricted optimisation can be performed.
- For two-arm three-period platform trials where the design is symmetrical with respect to sample sizes per period, the allocation in period 2 would be $1 : 1 : \sqrt{(2)}$
- If the entry time of Arm B is unknown, equal allocation will remain in the first period and the optimal allocation ratios for period 2 can be computed when Arm B enters the platform assuming the exit time of Arm A fixed.
- Other strategies and types of allocation could be considered, such as response-adaptive randomisation.

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Thank you!

GRÀCIES ESKERRIK ASKO GRAZAS GRACIAS!

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