Model-based Adjustments for Non-concurrent Comparisons in Platform Trials

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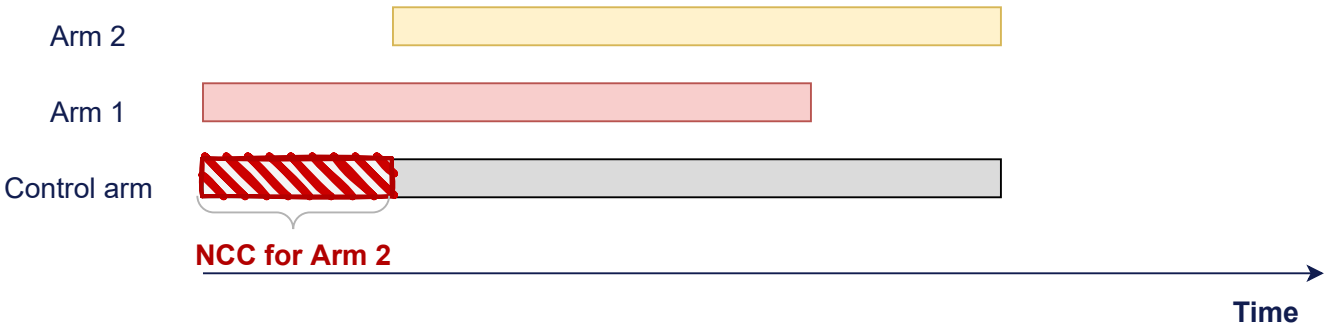
Reminder of the considered problem

Platform trials

Multi-arm adaptive trials that allow experimental treatment arms to enter and leave the trial at different times

Control groups in platform trials:

- **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



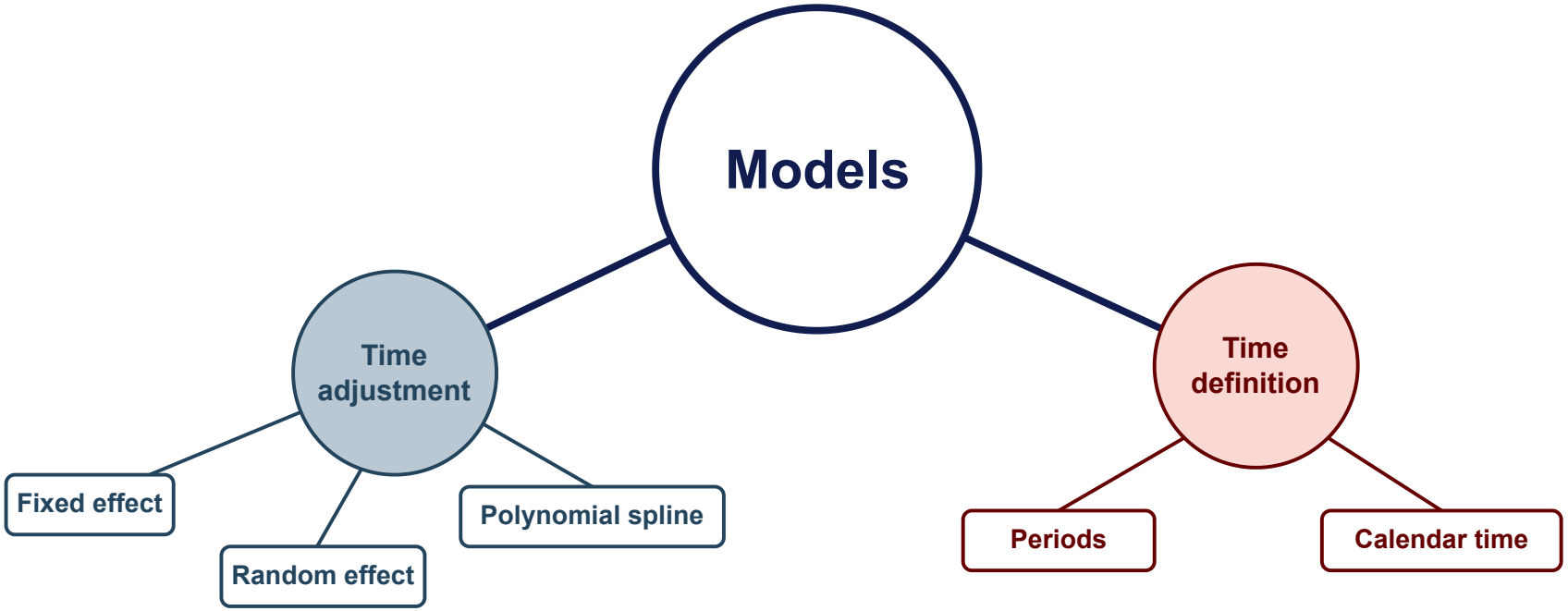
Challenges when using NCC:

- Bias in the estimates
- Type I error rate control

→ **Modelling approaches**

Goals and contributions of the thesis

1. **Generalize** the **model-based approaches** to trials with more than two experimental treatment arms
2. Consider **alternative definitions** of the **time covariate**
3. Propose **more flexible modeling approaches** for incorporating NCC
4. **Software** implementation in R



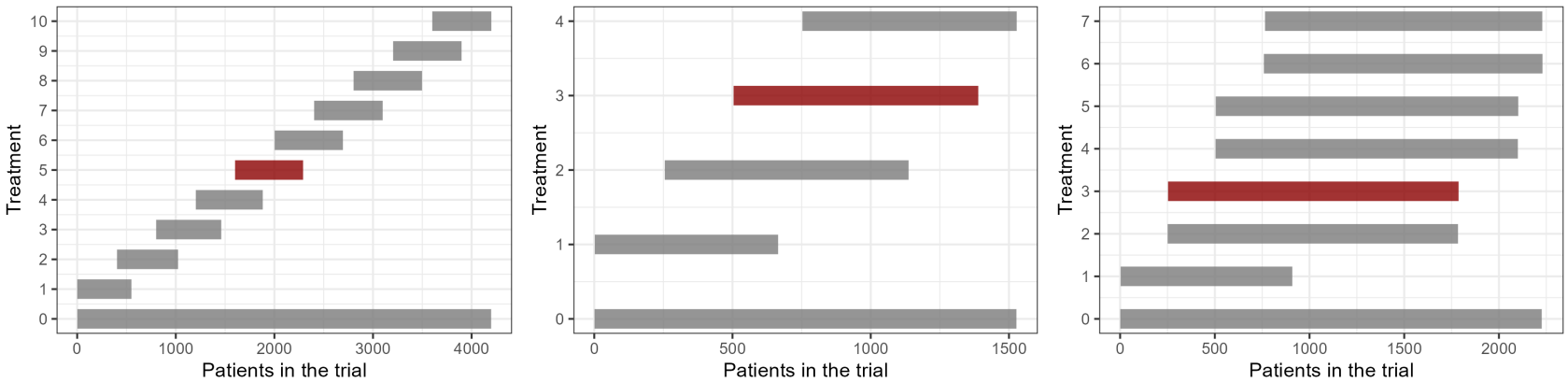
Today's talk: Results of a simulation study to investigate the operating characteristics of the proposed models

Simulation settings

- Consider platform trials with K experimental treatment arms ($K = 10$, 7 or 4)
- Evaluate the efficacy of arm M ($M = 5$ or 3)
- Use all data until arm M leaves the trial for the analysis
- Equal sample size $n = 250$ in each treatment arm
- New arm enters after $\mathbf{d} = (d_1, \ldots, d_K)$ patients are recruited to the trial
- Time trends of different patterns and strength λ

Hypothesis testing problem:

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

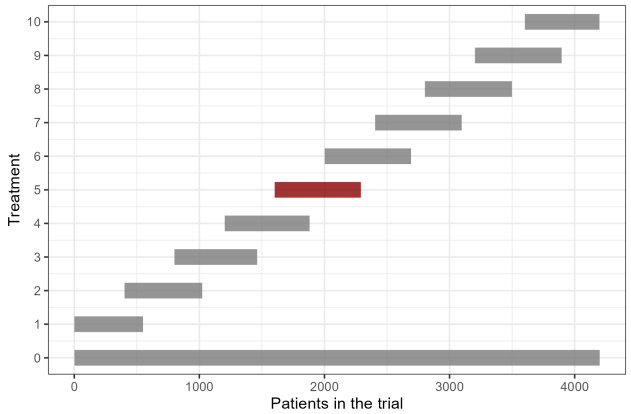


Part 1: Extension of regression model to trials with multiple arms

Adjust for periods in the trial as fixed effect:

$$y_j = \underbrace{\eta_0}_{\substack{\text{Control response} \\ \text{in period 1}}} + \underbrace{\sum_{k \in \mathcal{K}_M} \theta_k \cdot I(k_j = k)}_{\text{Treatment effects}} + \underbrace{\sum_{s=2}^{S_M} \tau_s \cdot I(s_j = s)}_{\text{Period time effects}} + \varepsilon_j$$

j . . . patient index in the order of enrollment time
$\mathcal{K}_M$ . . . set of active treatments in periods prior or up to S_M
S_M . . . period in which arm M finishes
$\varepsilon_j \sim \mathcal{N}(0, \sigma^2)$



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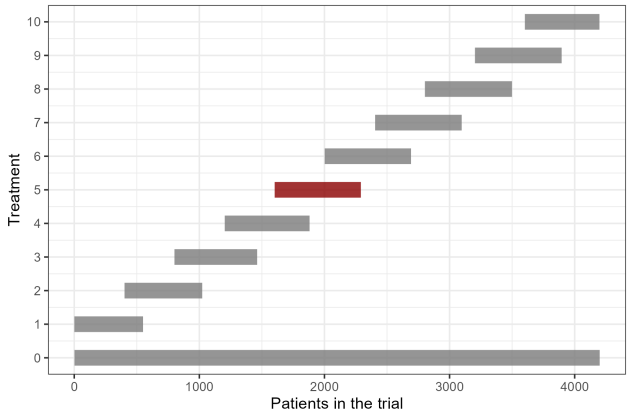
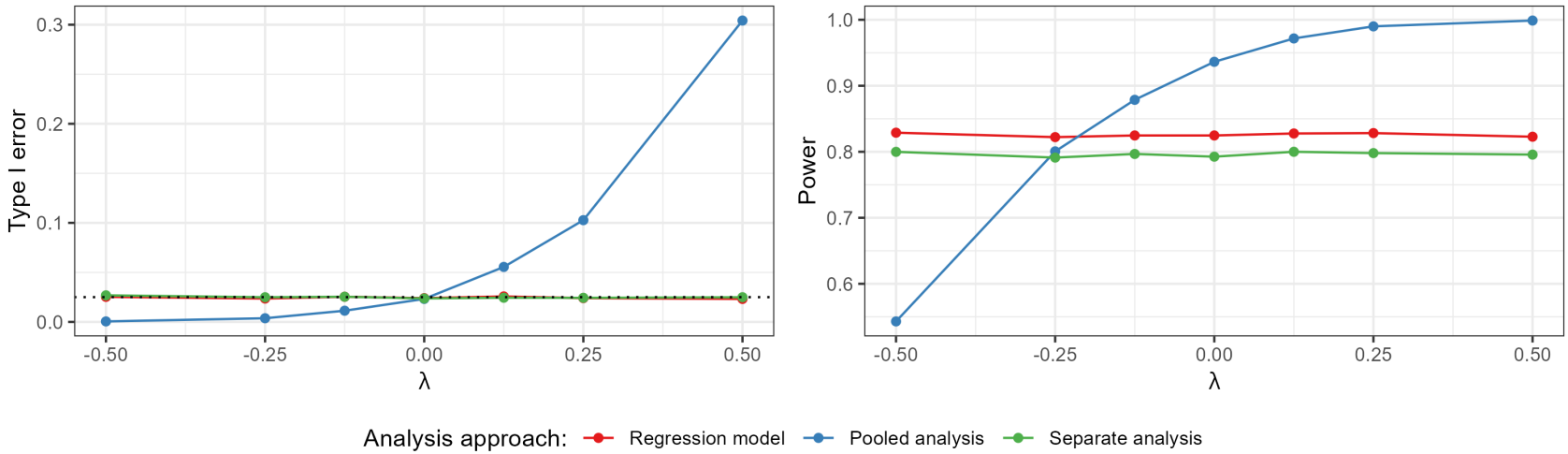
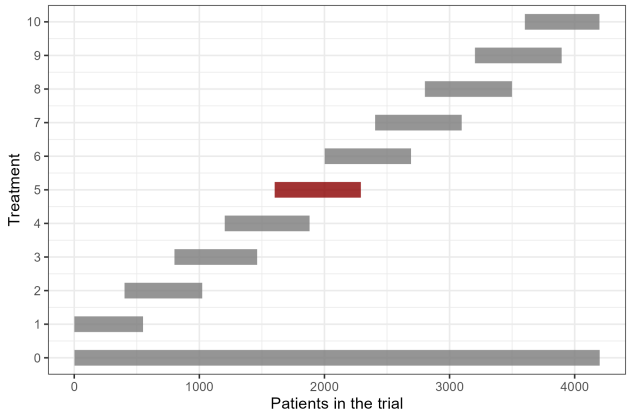


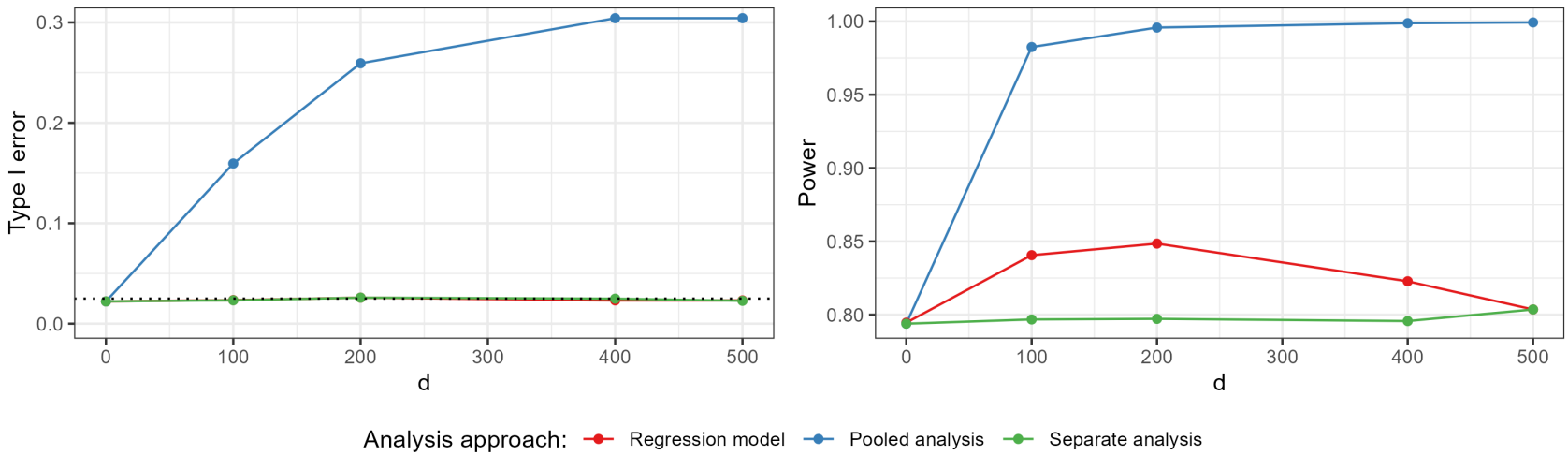


Impact of the timing of adding arms on the operating characteristics

Equidistant entry times: $d_i = d \cdot (i - 1)$



Varying d leads to different overlaps between the treatment arms, from complete overlap ($d = 0$) to no overlap ($d = 2n$).



The regression model only leads to power gain as compared to the separate analysis if there is some overlap between the treatment arms.

Part 2: Alternative definition of time covariate

Adjust for time as calendar time interval rather than period:

$$y_j = \underbrace{\eta_0}_{\substack{\text{Control response} \\ \text{in period 1}}} + \underbrace{\sum_{k \in \mathcal{K}_M} \theta_k \cdot I(k_j = k)}_{\text{Treatment effects}} + \underbrace{\sum_{c=2}^{C_M} \tau_c \cdot I(c_j = c)}_{\text{Calendar time effects}} + \varepsilon_j$$

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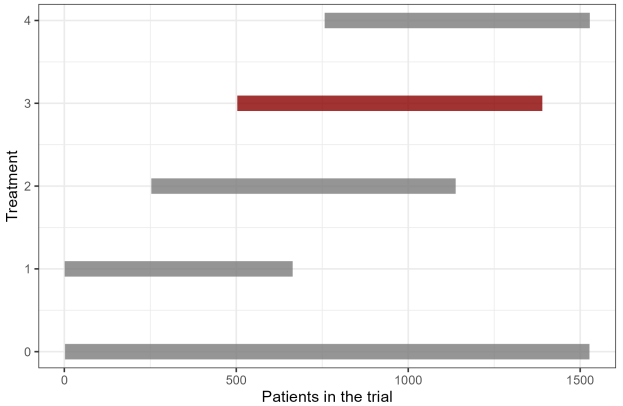

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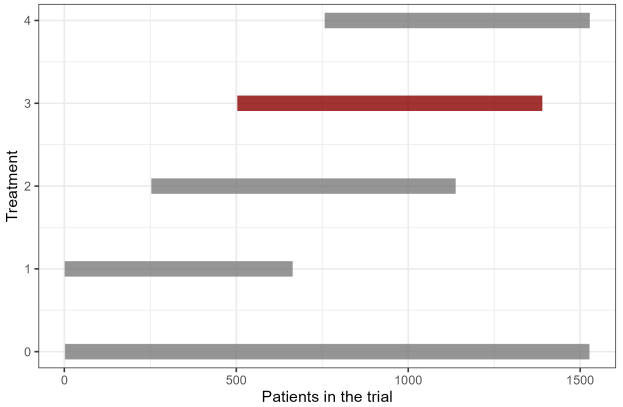

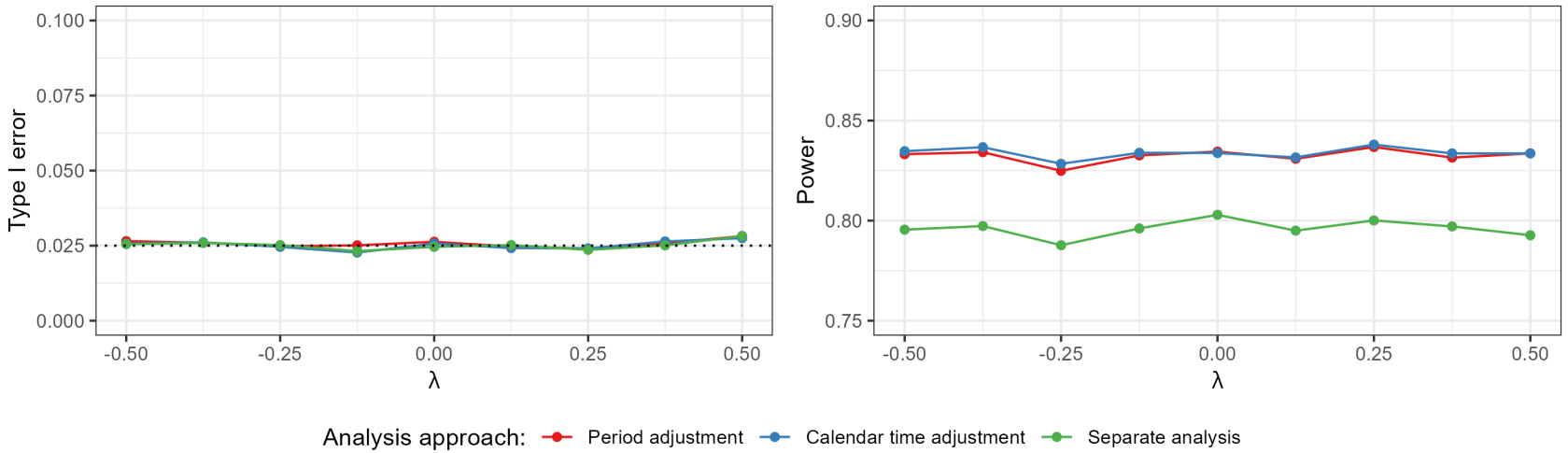

Part 3: More flexible modeling approaches: Cubic spline regression

Adjust for time with a spline function:

$$y_j = \underbrace{\eta_0}_{\substack{\text{Average} \\ \text{control response} \\ \text{across the trial}}} + \underbrace{\sum_{k \in \mathcal{K}_M} \theta_k \cdot I(k_j = k)}_{\text{Treatment effects}} + \underbrace{f(j)}_{\substack{\text{Spline function} \\ \text{of enrollment time}}} + \varepsilon_j$$

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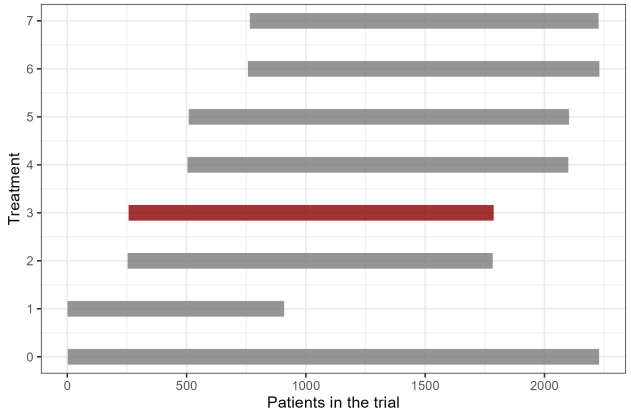

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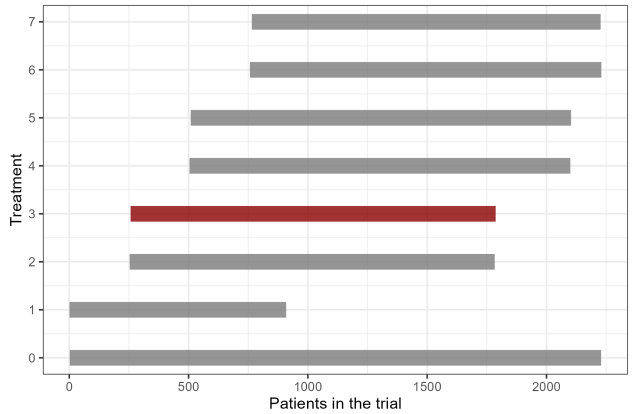
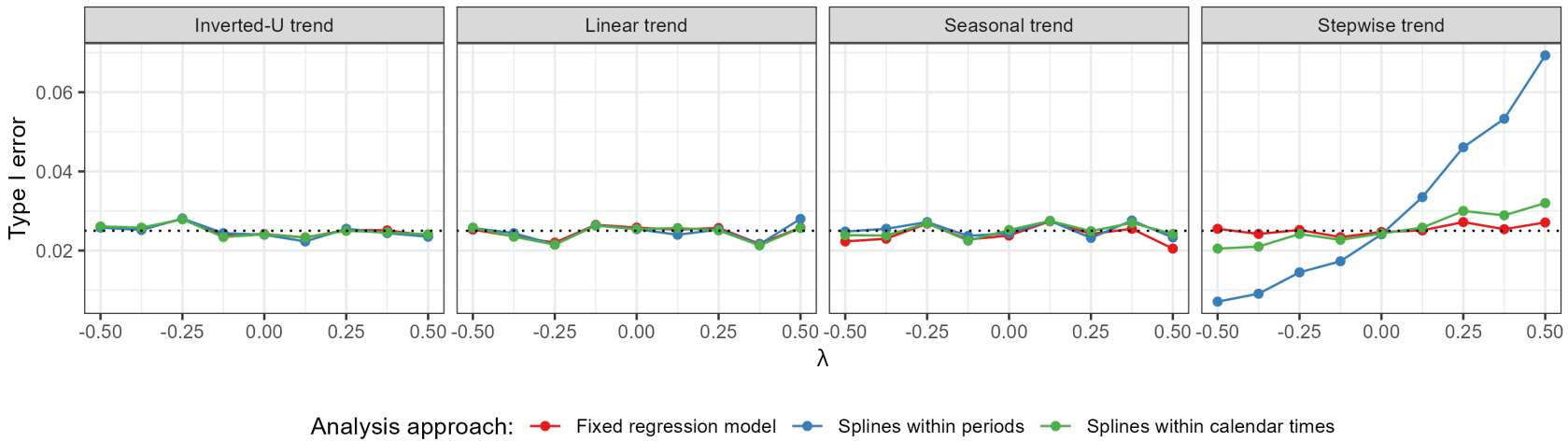




Conclusions and further results

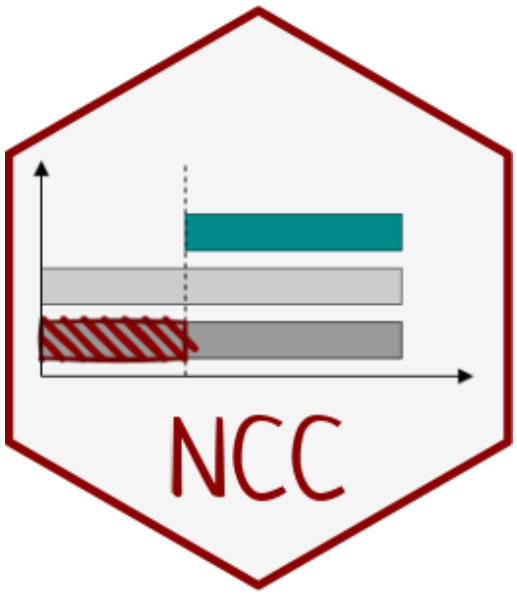
Key messages

- Non-concurrent controls may improve the statistical power, but can introduce bias due to time trends if not adjusted for
- Model-based approaches can increase the power as compared to the separate analysis, while controlling the type I error

Other findings

- Modelling approaches only lead to power gain as compared to the separate approach if there is some overlap between the treatment arms
- Larger power for treatment arms that were added later, as the size of NCC increases
- Choice of the calendar time length is crucial for type I error rate control
- Mixed models do not control the type I error in the investigated scenarios

R-package NCC



Models:

- Regression models with fixed effects: `fixmodel_cont()`
- Mixed models: `mixmodel_cont()`
- Spline regressions: `splines_cont()`
- Pooled and separate analysis: `poolmodel_cont()`, `sepmodel_cont()`

Data generation:

- Functions to simulate platform trials with continuous and binary outcomes: `datasim_cont()`, `datasim_bin()`

Simulation functions:

- Flexible wrapper functions to run multiple replications of desired scenarios in parallel: `sim_study_par()`, `all_models()`

Thank you for your attention!