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

Pavla Krotka

Supervisors: Martin Posch, Marta Bofill Roig

Master's Seminar, 28.11.2022

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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.

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

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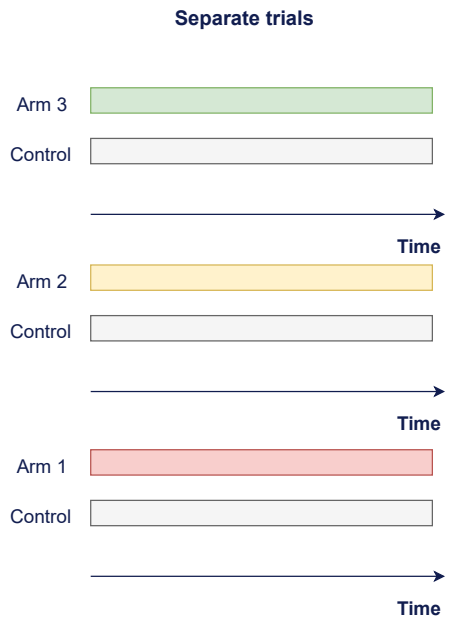

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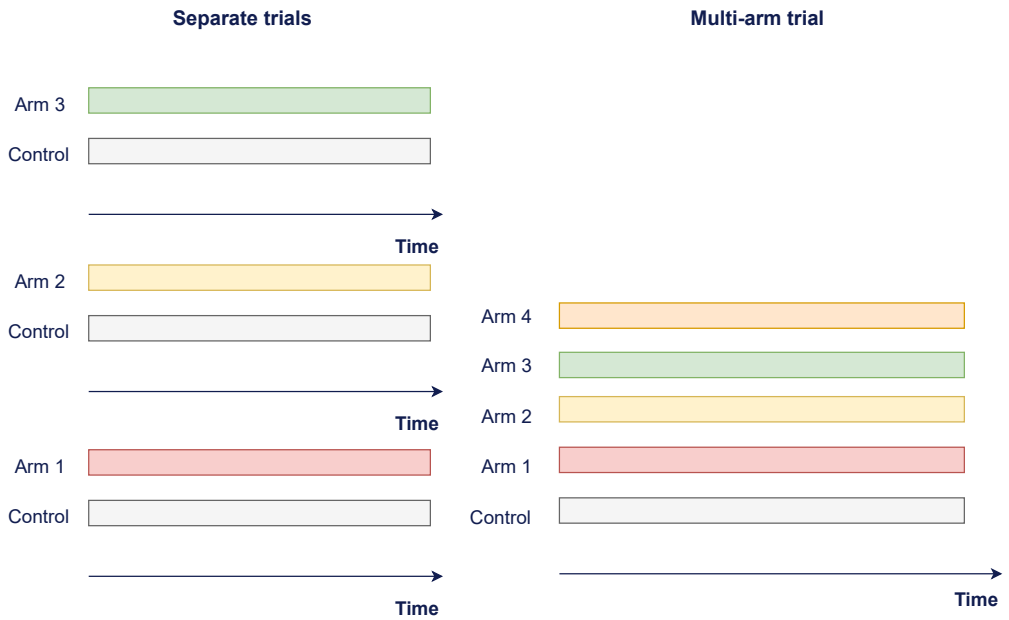

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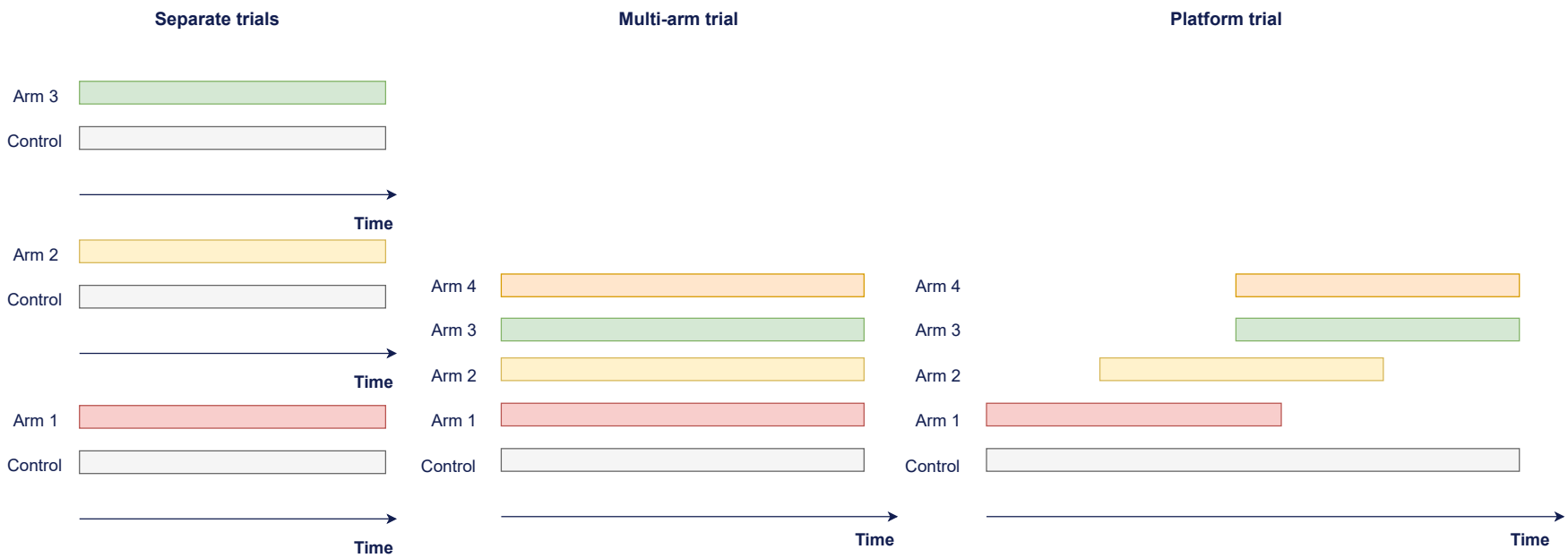

Platform trials

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
- Experimental treatments can enter the trial and be investigated as soon as they became available, which provides **more flexibility** than multi-arm trials

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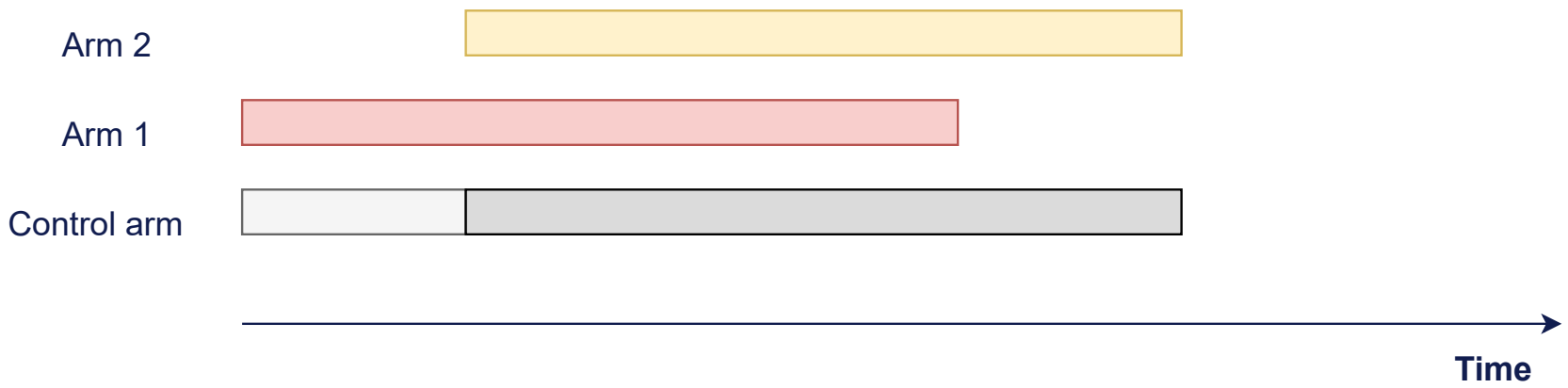
Challenges

- Multiple operational and statistical challenges due to **higher complexity**
- The entering and leaving times, as well as 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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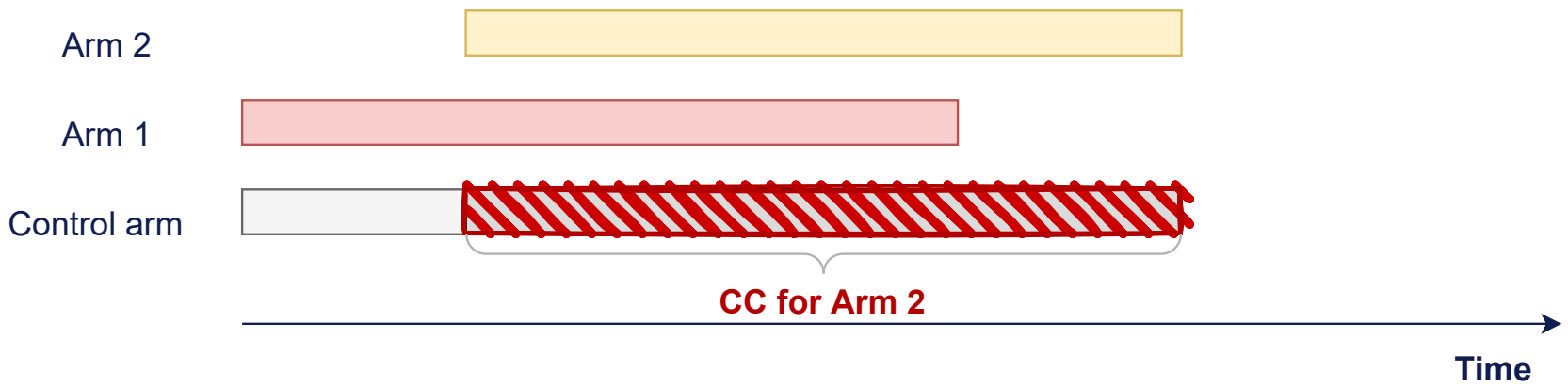

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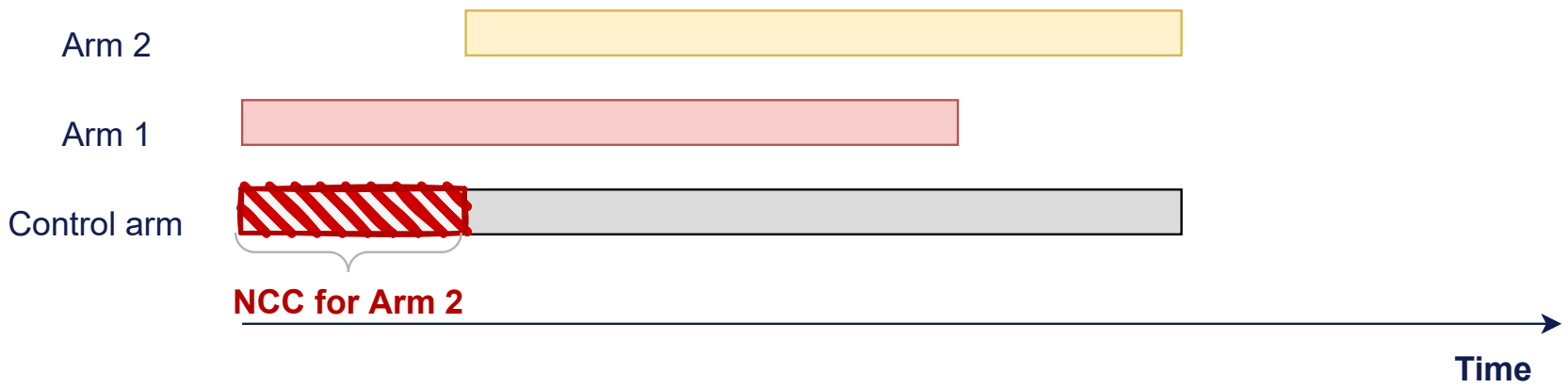

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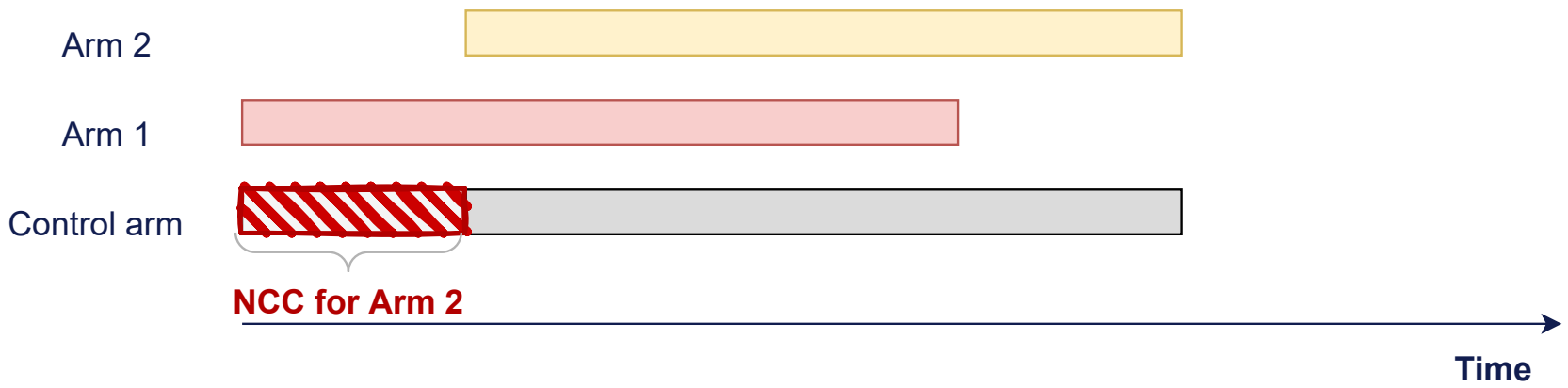
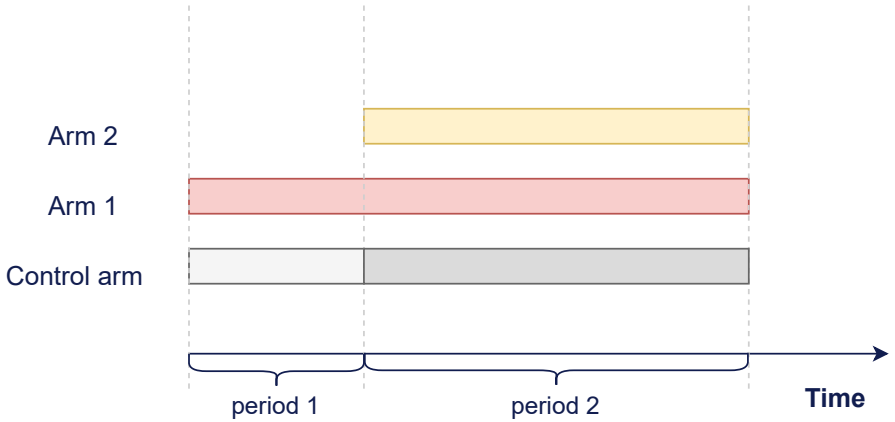


Incorporating non-concurrent controls can substantially improve the **efficiency** (increased statistical power due to **larger sample sizes**) but may introduce **bias** due to **time trends**.

State-of-the-art analysis methods



Hypothesis testing problem:

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

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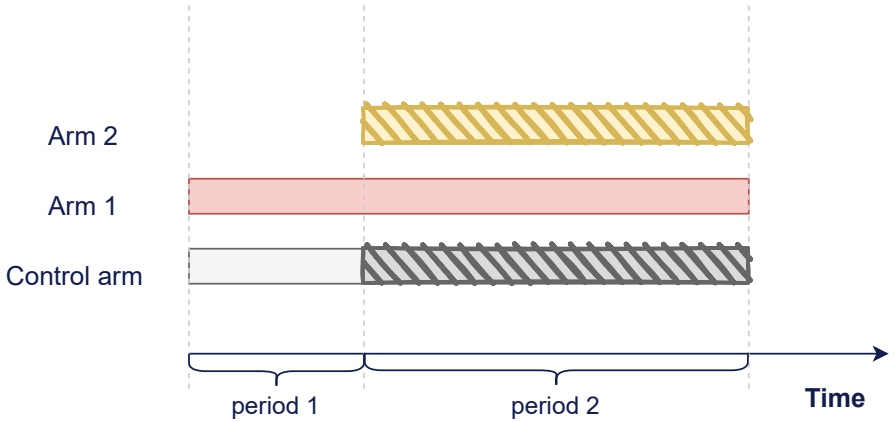

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Naive analysis methods

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

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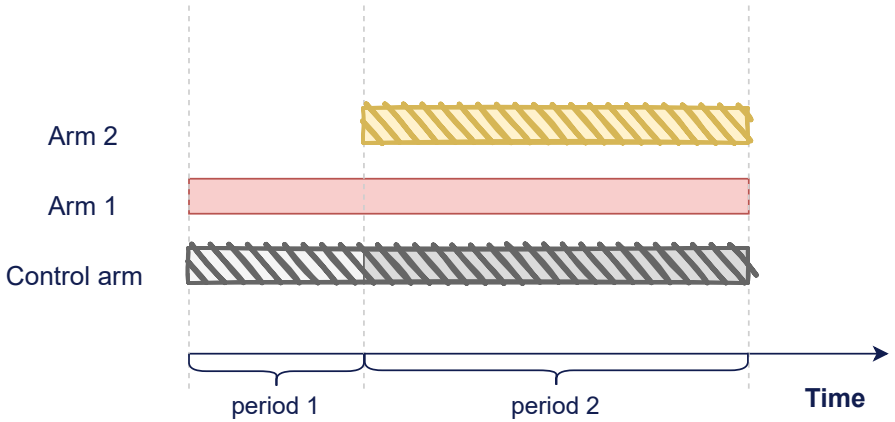

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Naive analysis methods

- **Separate approach:** analysis using only concurrent controls
- **Pooled approach:** pooling concurrent and non-concurrent controls

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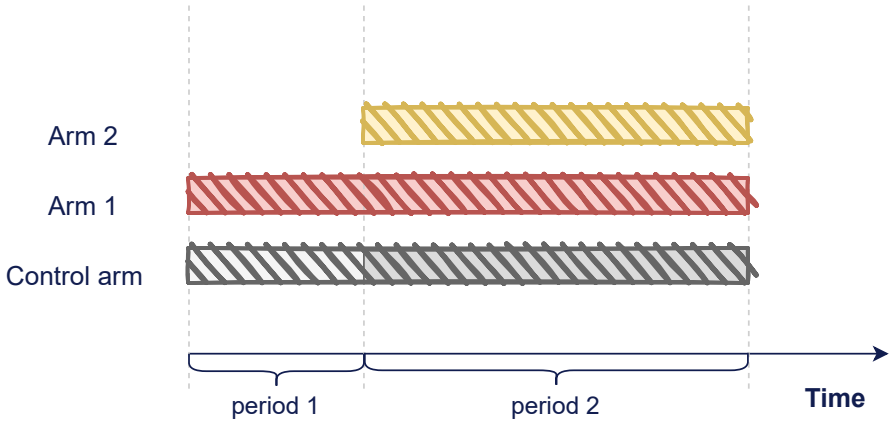

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Novel methods

- **Frequentist regression models:** adjust for time trends by including time as a covariate (Lee & Wason, 2020; Bofill Roig, Krotka, et al., 2022)
- **Bayesian Time Machine:** adjusts for time trends by smoothing over time bins using a second-order Bayesian normal dynamic linear model (Saville, et al., 2022)
- **Network meta-analysis:** uses meta-analysis techniques to combine information from different periods (Marschner & Schou, 2022)

Frequentist regression model

Adjust for time trends by a stepwise function in a regression model

$$E(X) = \eta_0 + \sum_{k=1,2} \theta_k \cdot I(T = k) + \tau \cdot I(S = 2)$$

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

- All data available in the platform is used to estimate the time trend
- Time trend is assumed constant in every period
- Time is assumed to have equal effect for all arms

Frequentist regression model

Bofill Roig *et al. BMC Medical Research Methodology* (2022) 22:228
https://doi.org/10.1186/s12874-022-01683-w

BMC Medical Research Methodology

RESEARCH Open Access

On model-based time trend adjustments in platform trials with non-concurrent controls

Marta Bofill Roig[1], Pavla Krotka[1], Carl-Fredrik Burman[2], Ekkehard Glimm[3,4], Stefan M. Gold[5,6,7], Katharina Hees[8], Peter Jacko[9,10], Franz Koenig[1], Dominic Magirr[3], Peter Mesenbrink[11], Kert Viele[12] and Martin Posch[1*]

Key messages

- Increase in power as compared to the separate approach
- Type I error control, if:
  - Equal time trends across arms
  - Time trend additive on model scale
  - Block randomization

Open questions

- How would the models perform in more general platform trials with more than two experimental treatment arms?
- Would more advanced modeling approaches improve the power while maintaining the type I error?

Goals and contributions of this thesis

1. **Generalize** the **model-based approaches** to trials with more than two experimental treatment arms

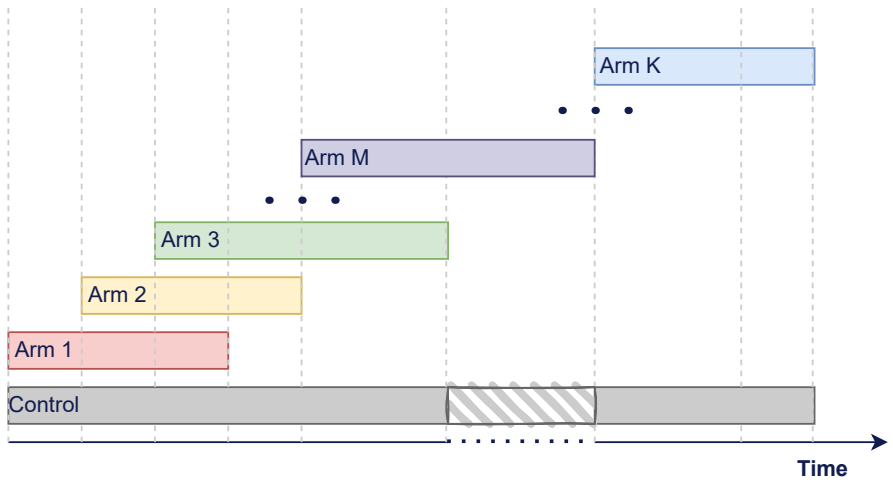
2. Propose **alternative models** for incorporating NCC
   - Consider alternative definitions of the time variable
   - Consider more flexible methods to estimate the time trend

3. Investigate the **operating characteristics** of the proposed approaches in a simulation study

4. **Software** implementation in R

Considered design

- Consider platform trials with K experimental treatment arms ($K > 2$)
- Statistical inference for arm $M \in \{1, \ldots, K\}$
- Use all data until arm M leaves the trial for the analysis



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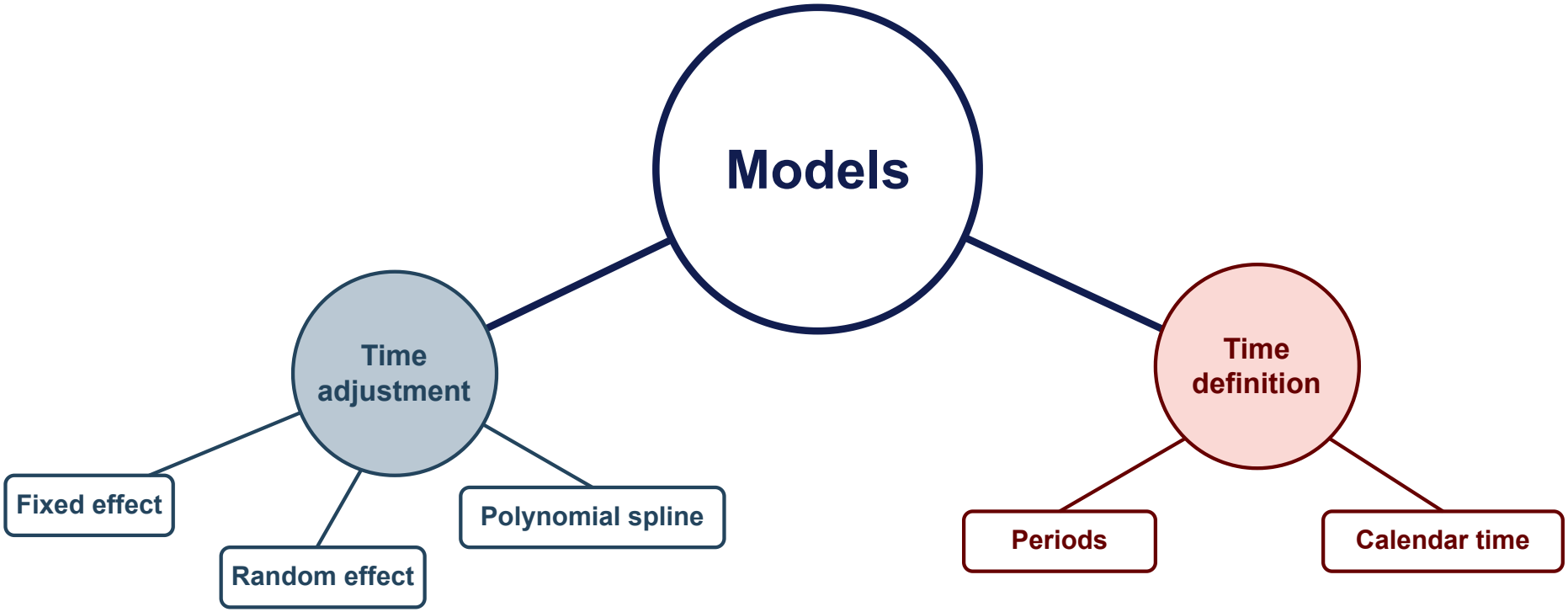
Investigated models



Regression model for trials with multiple arms

Adjust for time as fixed effect:

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

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

- Extension of the model considered in Bofill Roig, Krotka, et al. (2022)
- The model uses all data available in the trial until arm M leaves, including data from unfinished arms

Mixed models

Adjust for time as random effect:

$$y_j = \underbrace{\eta_0}_{\substack{\text{Average control} \\ \text{response across the trial}}} + \underbrace{\sum_{k \in \mathcal{K}_M} \theta_k \cdot I(k_j = k)}_{\text{Treatment effects}} + \underbrace{\sum_{s=2}^{S_M} u_s \cdot I(s_j = s)}_{\text{Period time effects}} + \varepsilon_j$$

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

Investigated variants:

- Uncorrelated random effects
- Autocorrelated (AR1) random effects

Spline regression

Adjust for time with a spline function:

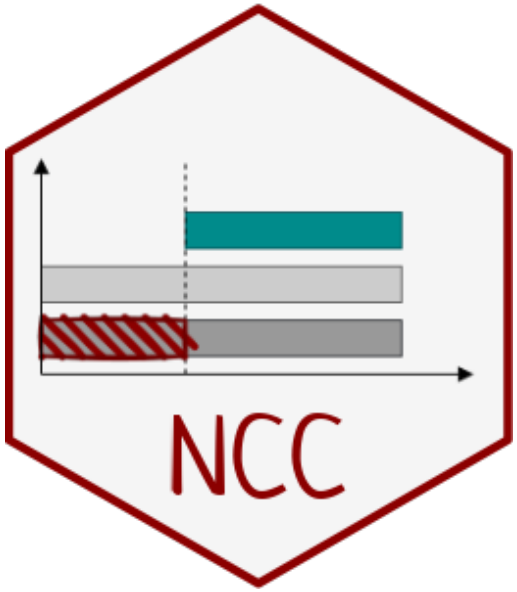
$$y_j = \underbrace{\eta_0}_{\substack{\text{Average control} \\ \text{response across the trial}}} + \underbrace{\sum_{k \in \mathcal{K}_M} \theta_k \cdot I(k_j = k)}_{\text{Treatment effects}} + \underbrace{f(j)}_{\substack{\text{Spline function} \\ \text{of enrollment time}}} + \varepsilon_j$$

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

Investigated variants:

- Define the knots according to periods or calendar times
- Consider linear, quadratic and cubic splines

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()`

Simulation study

Goals

- Inference for an added treatment arm M using NCC
- Evaluate the operating characteristics of the considered approaches:
  - Type 1 error
  - Statistical power
  - Bias of the treatment effect estimates
- State conditions under which the investigated methods lead to valid statistical inference

Setting

- Continuous endpoints
- Equal sample size n in each treatment arm
- Trials with $K > 2$ arms entering sequentially after every d patients recruited to the trial
- Time trends for each arm of different strength and following patterns:
  - Linear
  - Stepwise
  - Inverted-U

Selected references

- **Krotka, P.**, Bofill Roig, M., Hees, K., Jacko, P., Magirr, D. (2022). *"NCC: Simulation and analysis of platform trials with non-concurrent controls."* R package: https://github.com/pavlakrotka/NCC, Web-page: https://pavlakrotka.github.io/NCC/.
- Bofill Roig, M., **Krotka, P.**, et al. *"On model-based time trend adjustments in platform trials with non-concurrent controls."* BMC medical research methodology 22.1 (2022): 1-16
- Lee, K. M., and Wason, J. *"Including non-concurrent control patients in the analysis of platform trials: is it worth it?."* BMC medical research methodology 20.1 (2020): 1-12.
- Saville, B. R., Berry, D. A., et al. *"The Bayesian Time Machine: Accounting for Temporal Drift in Multi-arm Platform Trials."* Clinical Trials 19.5 (2022): 490-501
- Marschner, I. C. and Schou, I. M. *"Analysis of adaptive platform trials using a network approach."* Clinical Trials 19.5 (2022): 479-489
- Woodcock, J., and LaVange, L. M. *Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both.* New England Journal of Medicine 377.1 (2017): 62–70

Thank you for your attention!