On the Use of Non-concurrent Controls in Platform Trials

Pavla Krotka, Marta Bofill Roig, Franz Koenig, Martin Posch

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MEDICAL UNIVERSITY
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Acknowledgements

- EU-PEARL Project
- NCC Working Group

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Outline

Classical Clinical Trials

Classical Randomized Controlled Trials

- Gold standard for evaluating **efficacy** in drug development
- Investigating **one drug** to treat **single disease**
- One group receives the **new treatment**, another group (**control group**) receives a **placebo** or standard care
- Differences in outcomes between these groups are then assessed

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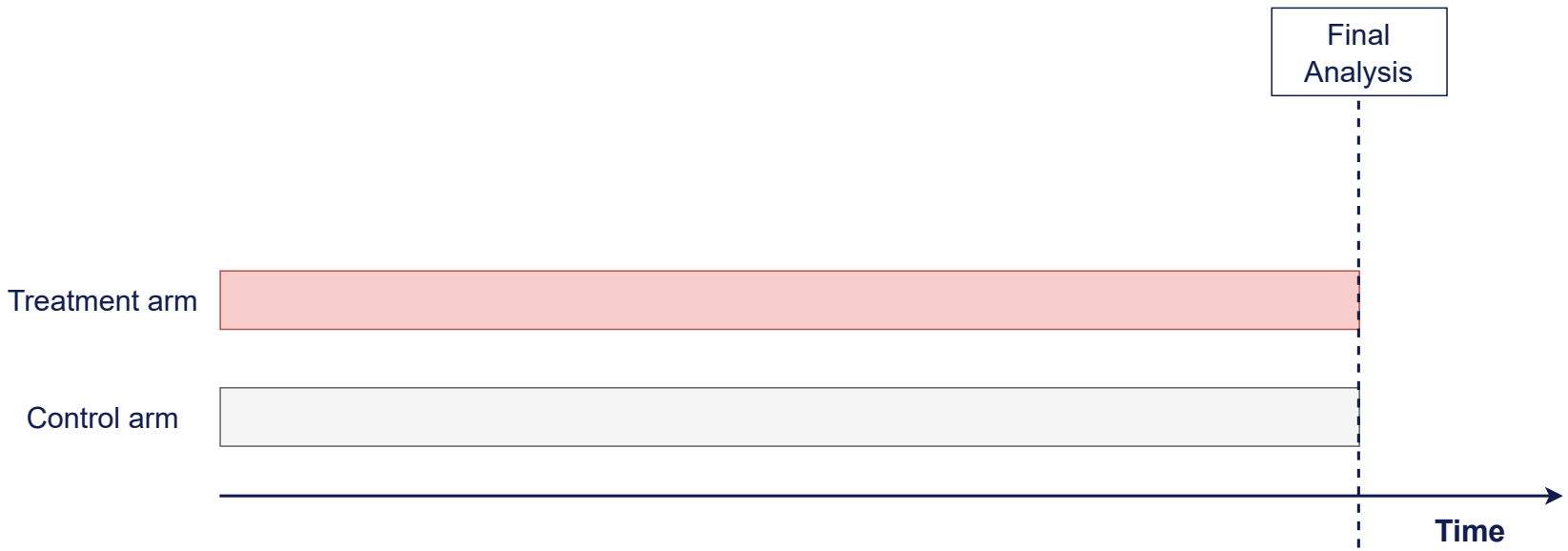

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Randomization

- Patients are **allocated randomly** among compared treatments
- Guarantees that assigned treatment is **independent of baseline characteristics**
- Produces **comparable groups** with regard to risk factors

Classical Clinical Trials

Benefits

- Most reliable form of **scientific evidence** for evaluating drug efficacy
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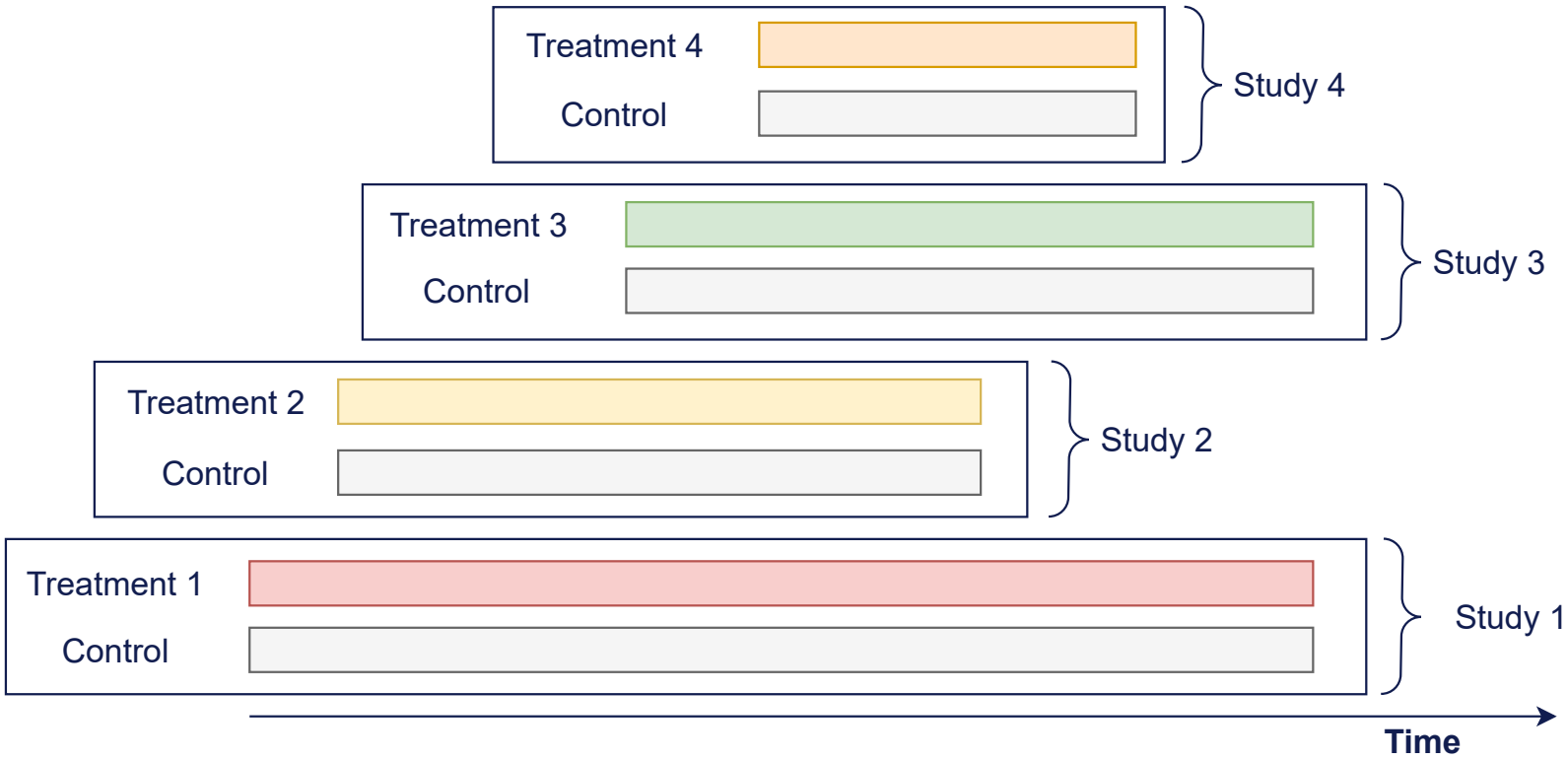
Challenges

- The conduct of an RCT takes a lot of **time**, usually several years
- RCTs can be very **expensive** and take a big part of the budget for drug development
- Similar trials are often done **simultaneously** by different companies
- RCTs often require **large sample sizes** to detect differences between groups and each trial requires its own treatment and control group

Classical Clinical Trials

Testing multiple treatments within a classical drug development program:



Adaptive Platform Trials

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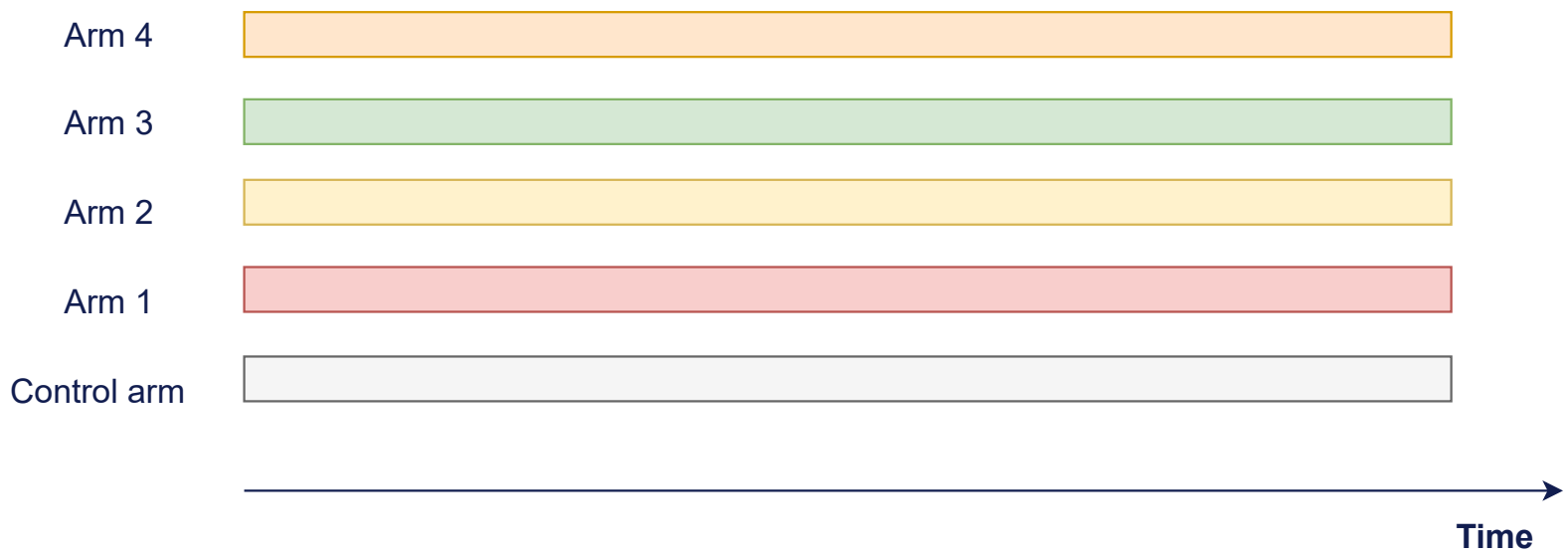

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- **Multi-arm multi-stage** trials
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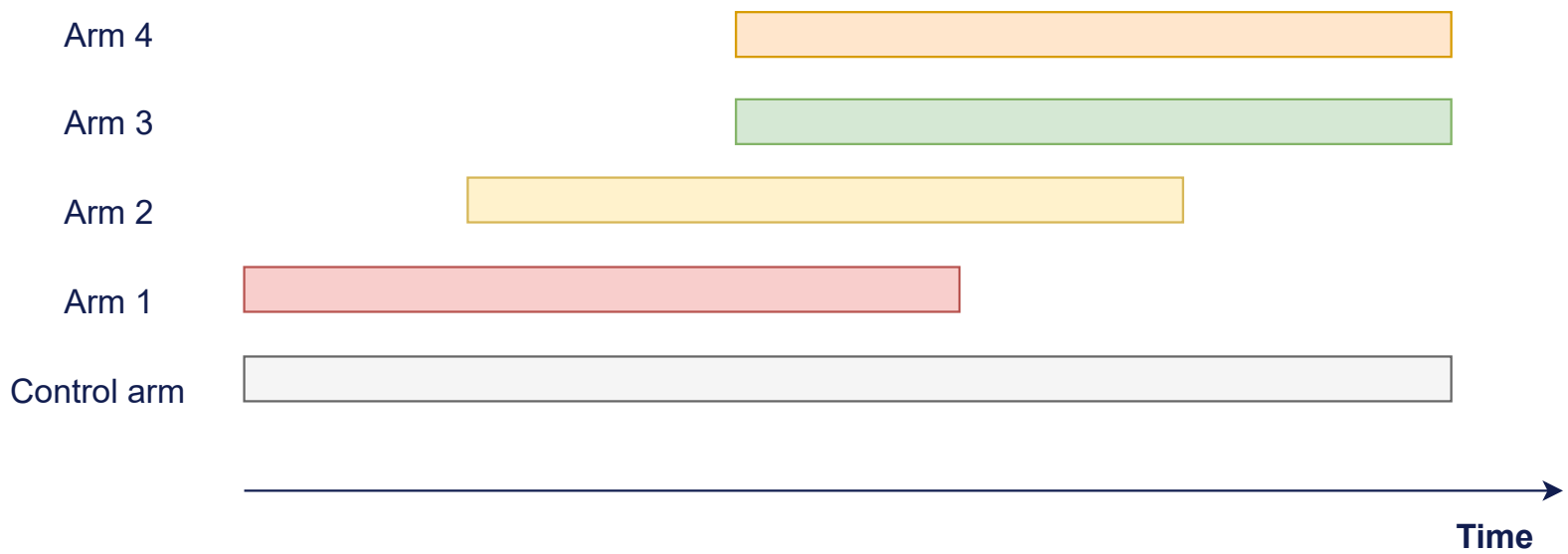
- New experimental treatment arms are allowed to **enter and leave** the trial at different times



Adaptive Platform Trials

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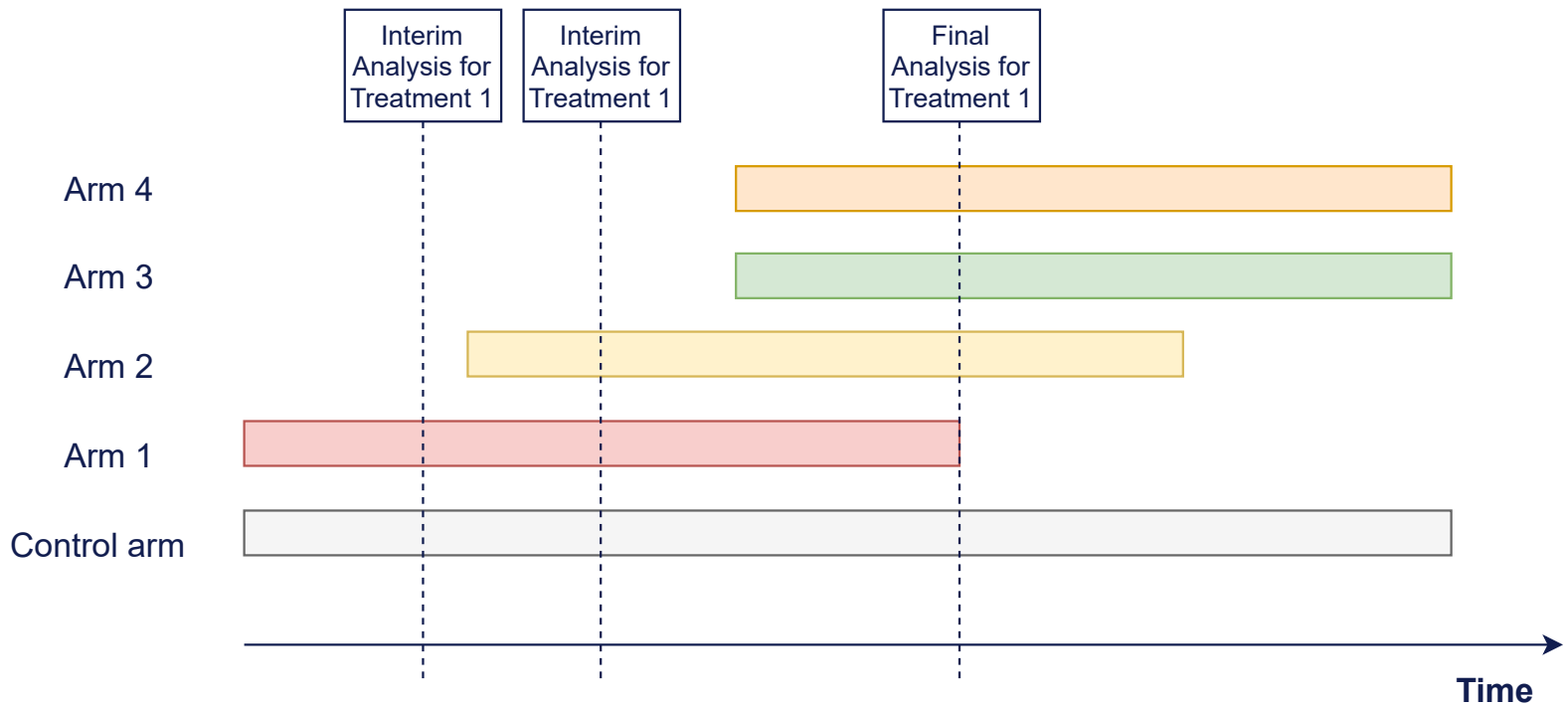
- **Multi-arm multi-stage** trials
- Flexible number of treatment arms and **shared controls**
- New experimental treatment arms are allowed to **enter and leave** the trial at different times
- Flexible number of **interim analyses**



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Benefits

- Treatments are developed **faster**, as drugs are tested **in parallel**
- Trials are **more efficient** thanks to shared resources and infrastructure
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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 in **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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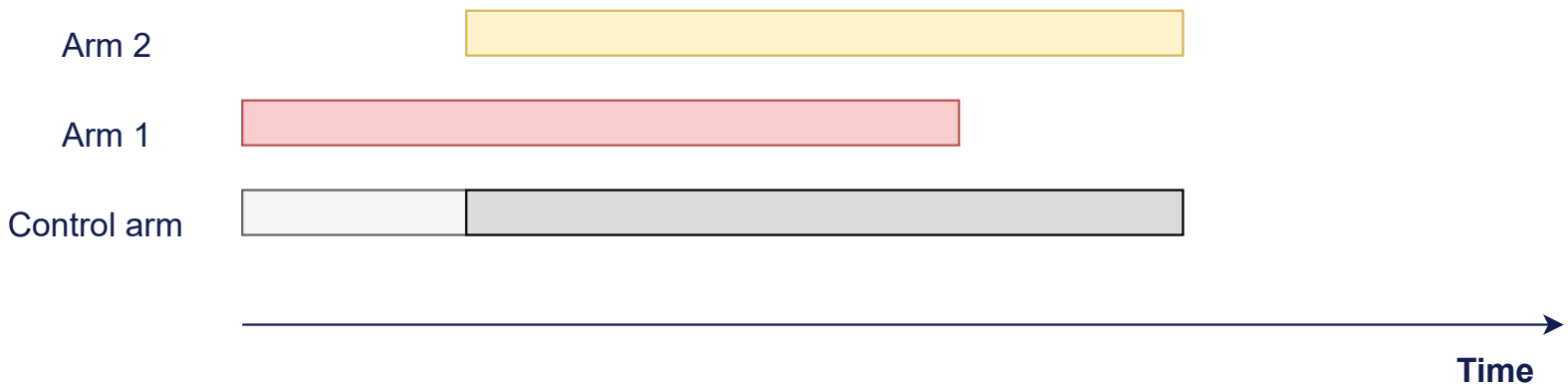

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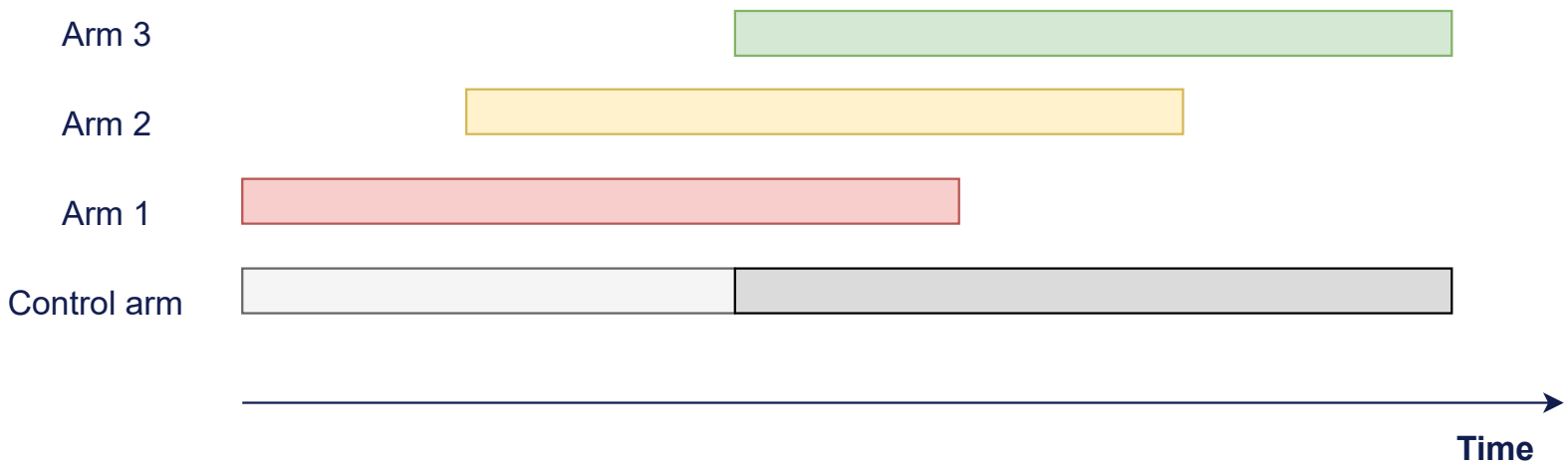

Control Groups in Platform Trials

Challenges

- Non-concurrent controls have been **randomized** too but in different sets of treatments and calendar times
- 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**

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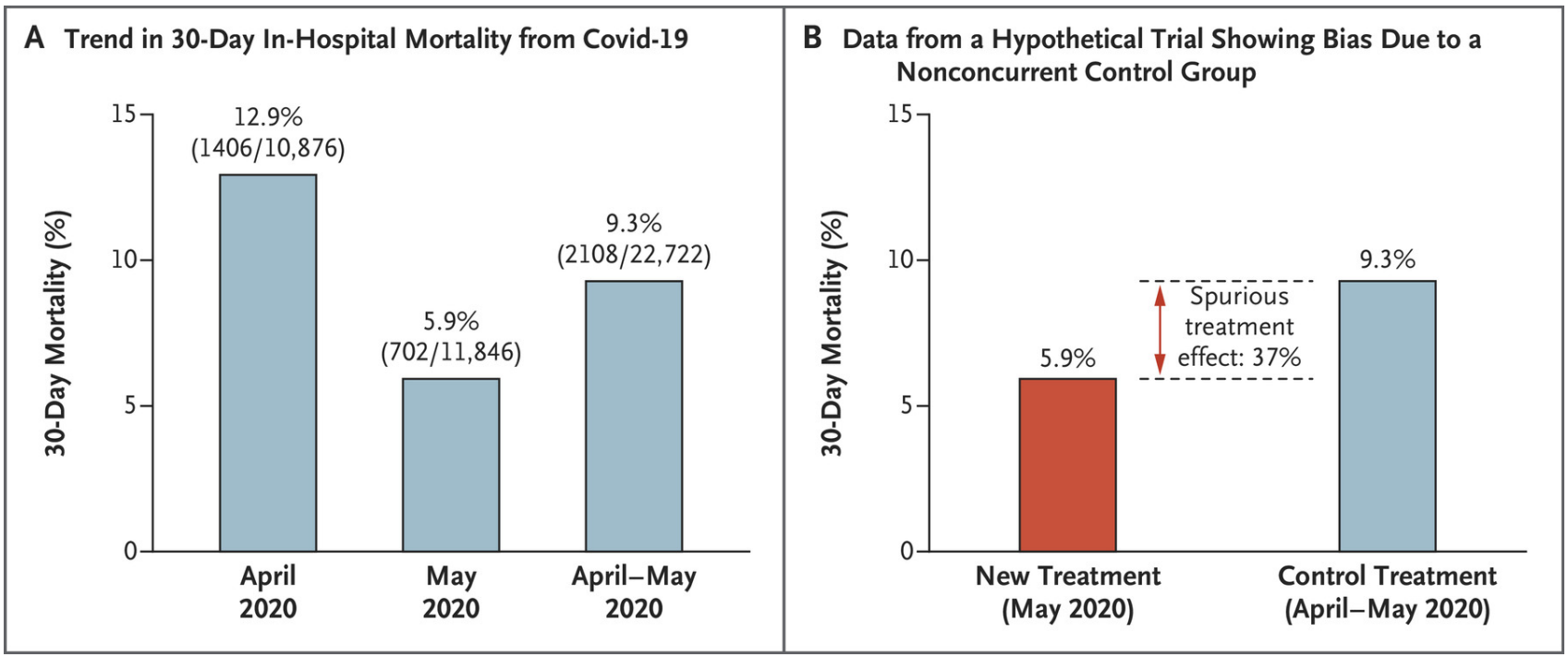
Factors influencing time trends

- Changes in **standard of care**
- Changes in **patient population**
- **Seasonal effects**
- **Pandemics**

What could go wrong?

Hypothetical example of how non-concurrent randomization could bias the results of a trial[1]:



[1] Dodd, L. E., Freidlin, B., & Korn, E. L. (2021). Platform Trials - Beware the Noncomparable Control Group. *New England Journal of Medicine*

Methods for Incorporating Non-concurrent Controls

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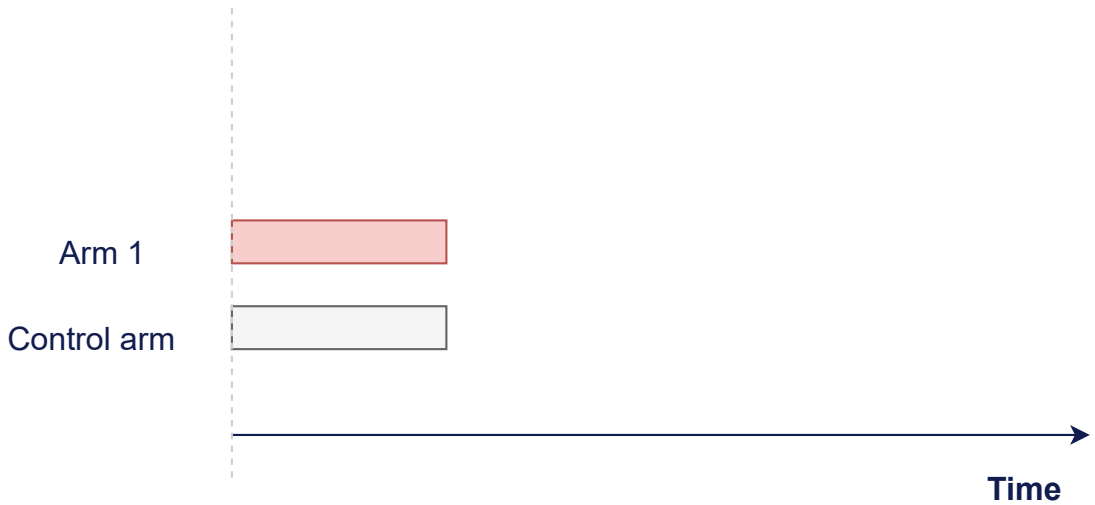
Example trial scheme

- One initial treatment arm (Arm 1)



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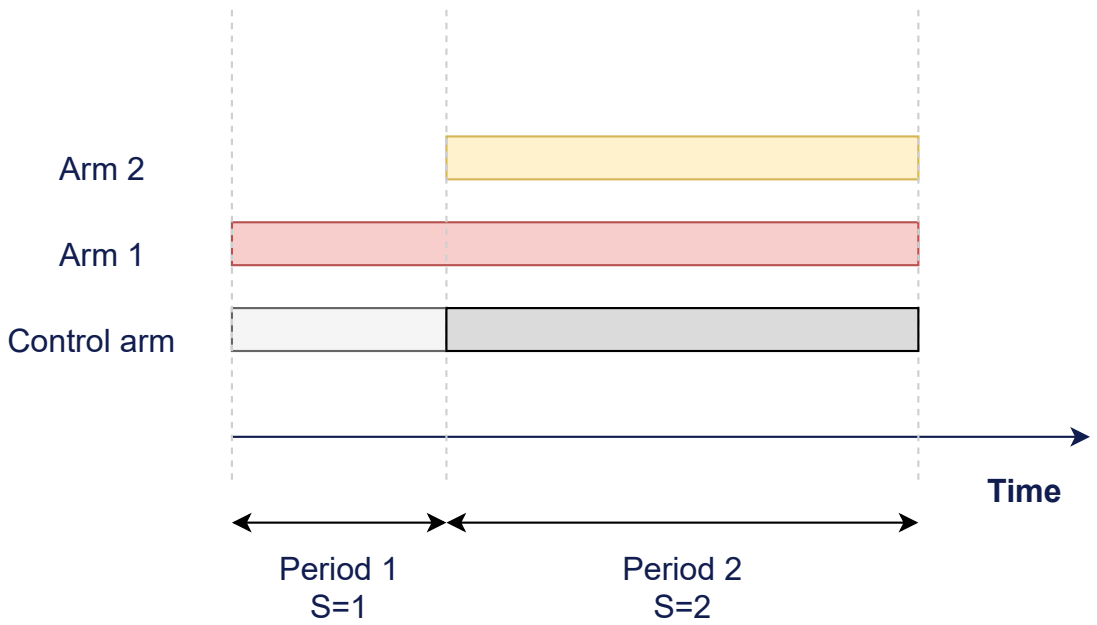

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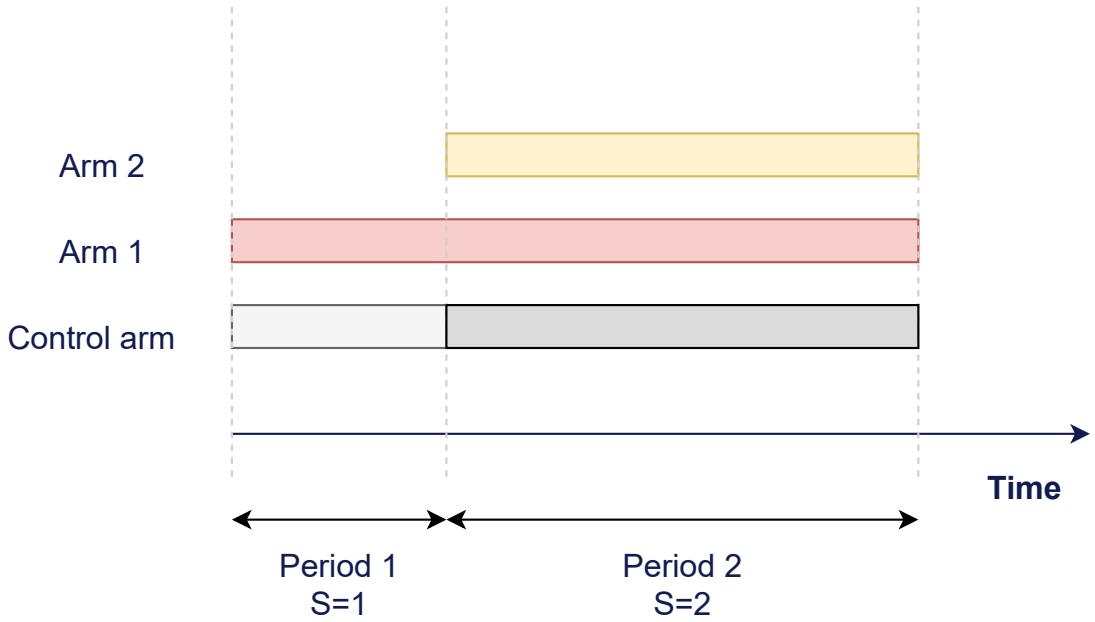

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$$H_0 : \theta_2 = 0$$
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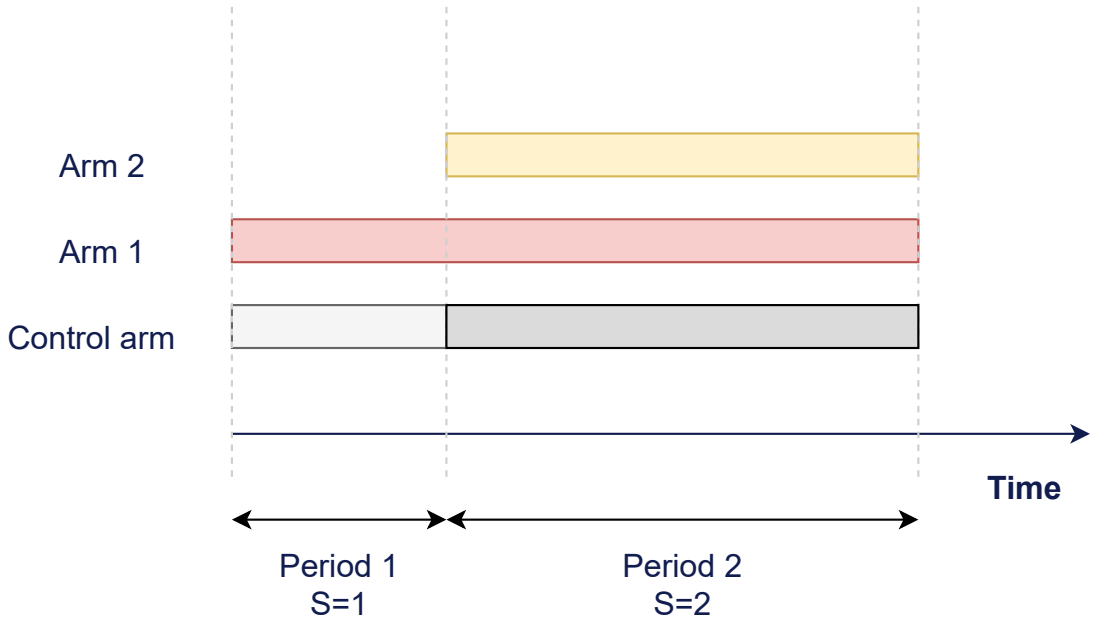

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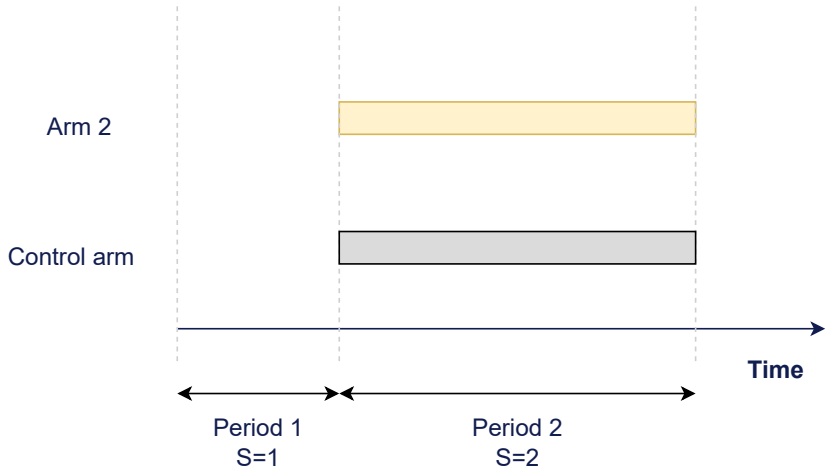
Standard approaches

Separate approach

- Analysis using **only concurrent** controls
- Controls the type I error regardless of time trends



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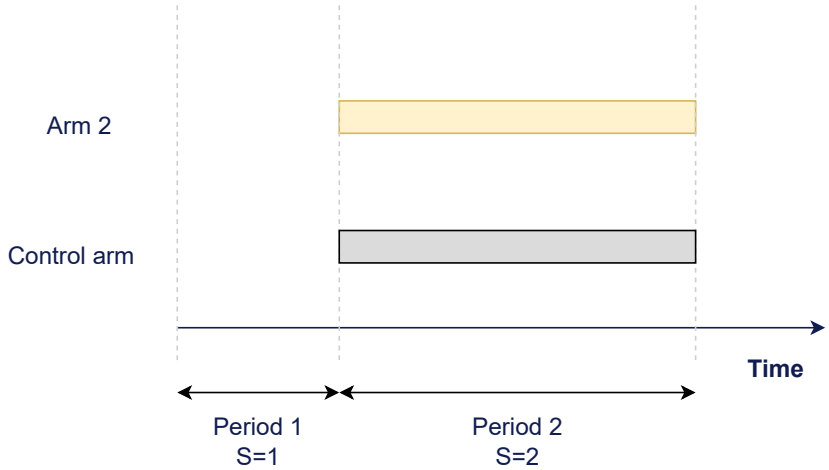
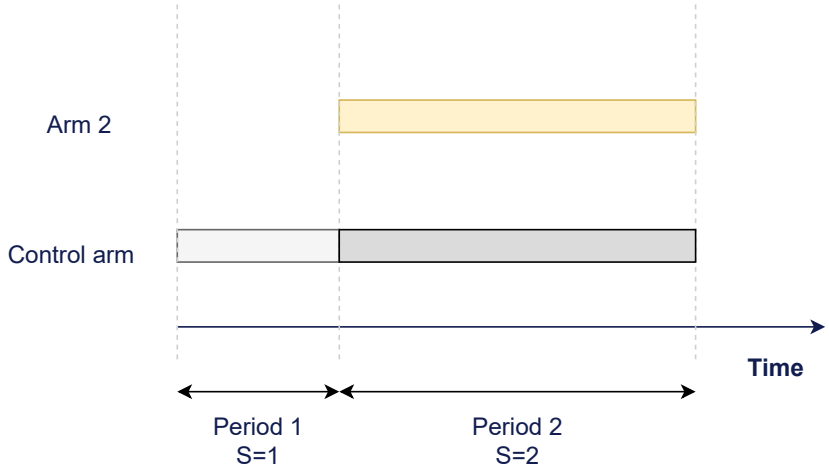


Pooled approach

- Pooling **concurrent and non-concurrent** controls
- Controls the type I error if there are no (positive) time trends in the control group



Model-based approaches

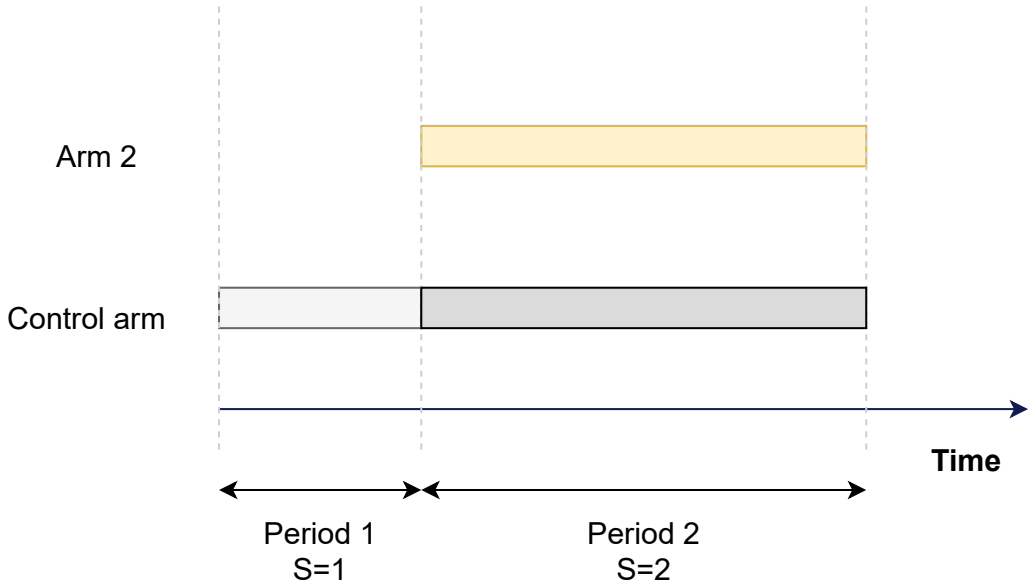
Individual model for each treatment arm

Using data from treatment arm 2 only [2]

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

$$E(X) = \underbrace{\eta_0 + \theta_2 \cdot I(T=2)}_{\text{Baseline and treatment effect}} + \underbrace{\tau \cdot I(S=2)}_{\text{Period time effect}}$$

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



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Model-based approaches

Joint model for all treatment arms

Using data from all treatment arms and control [2]

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

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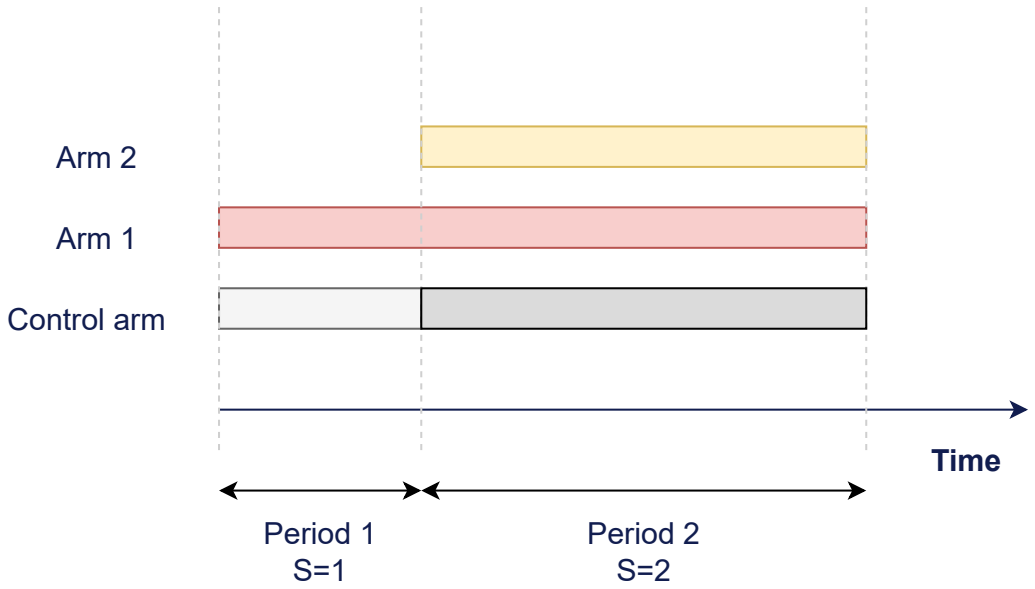

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Performance of the Considered Approaches

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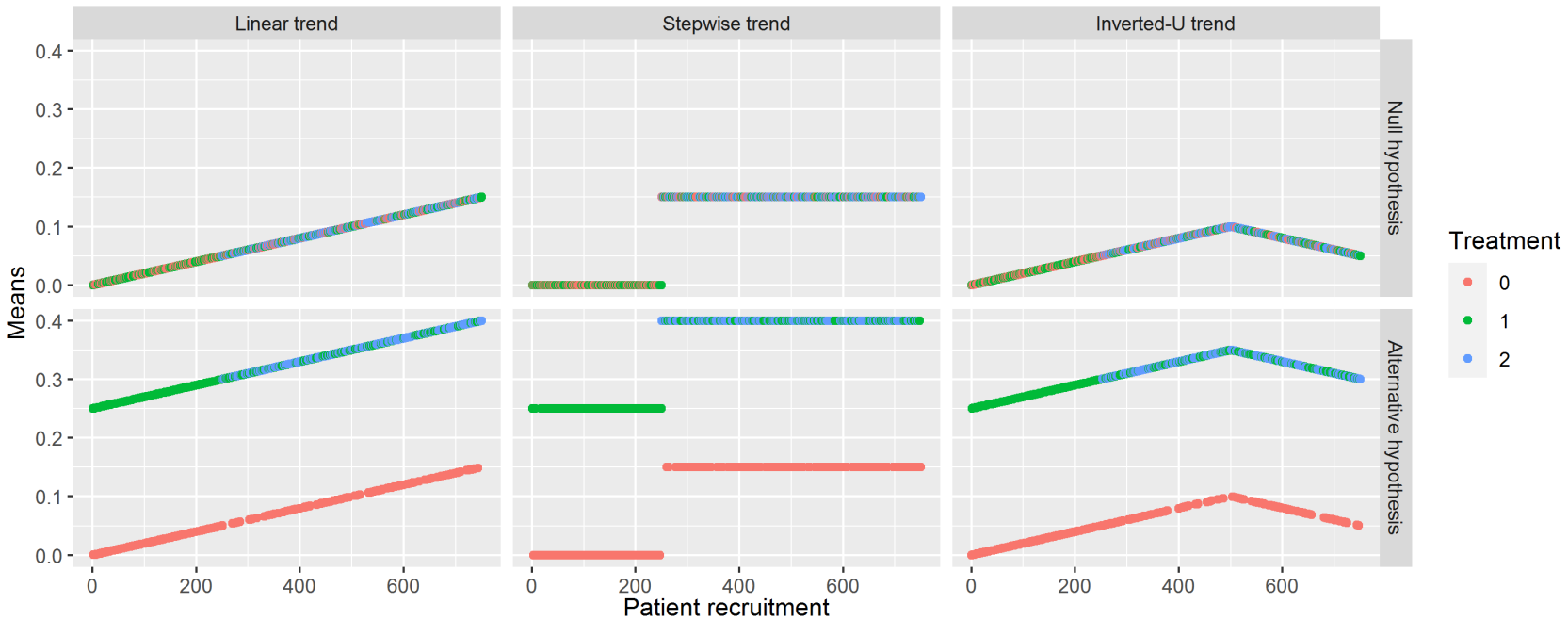
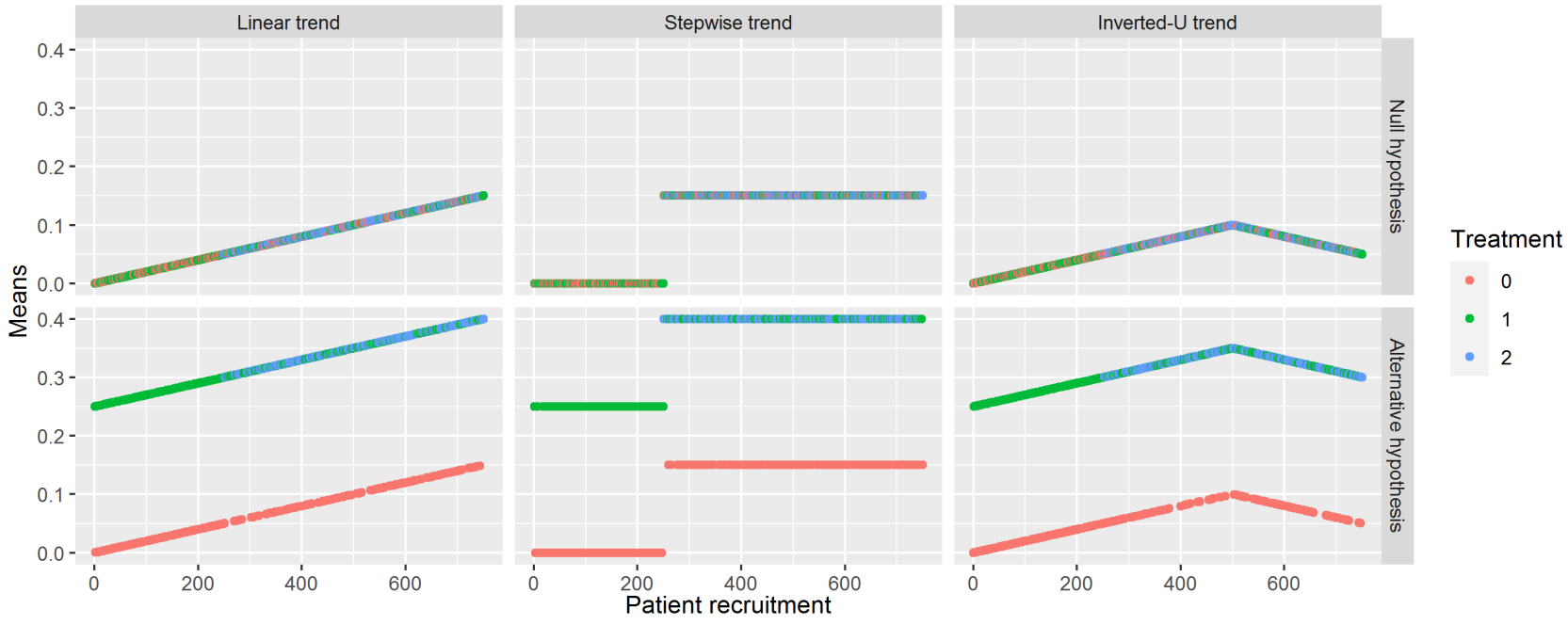
- 3 possible time trend patterns:



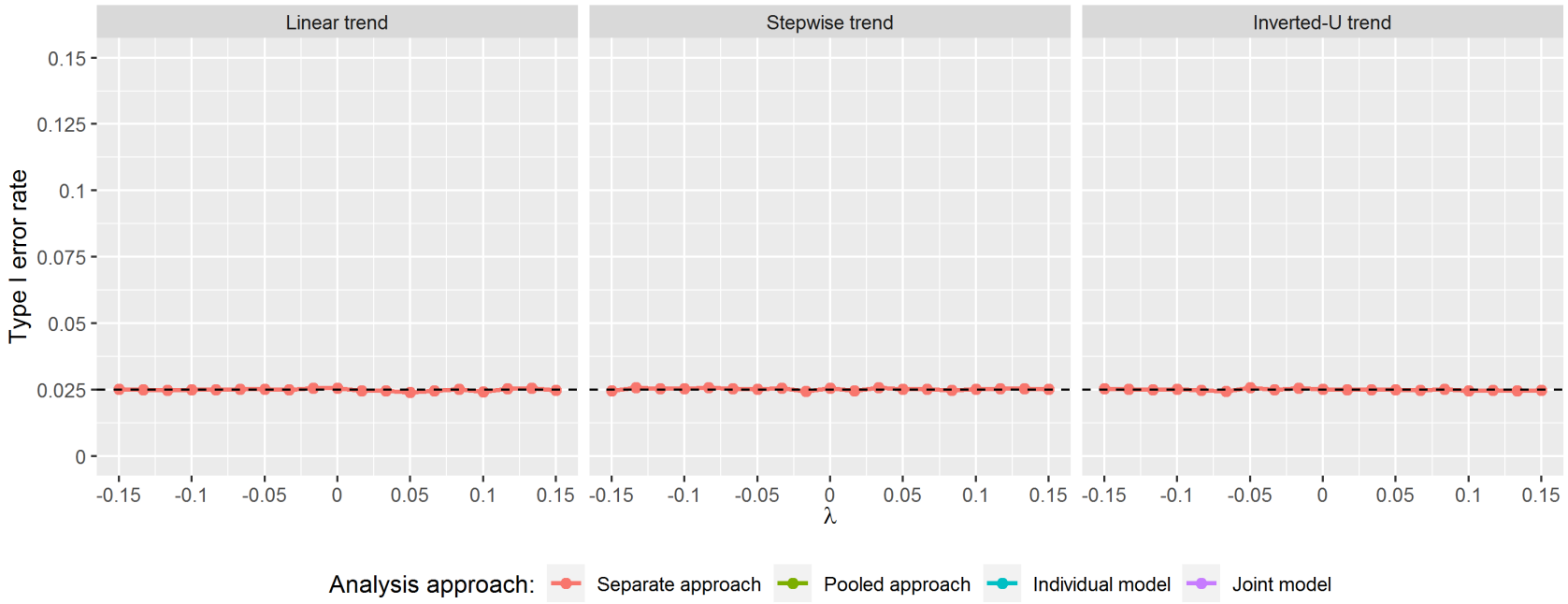
Scenarios with equal time trends



Equal time trends for control and both treatment arms ($\lambda_0 = \lambda_1 = \lambda_2$).

Performance for continuous endpoints with equal time trends

Type I error rate



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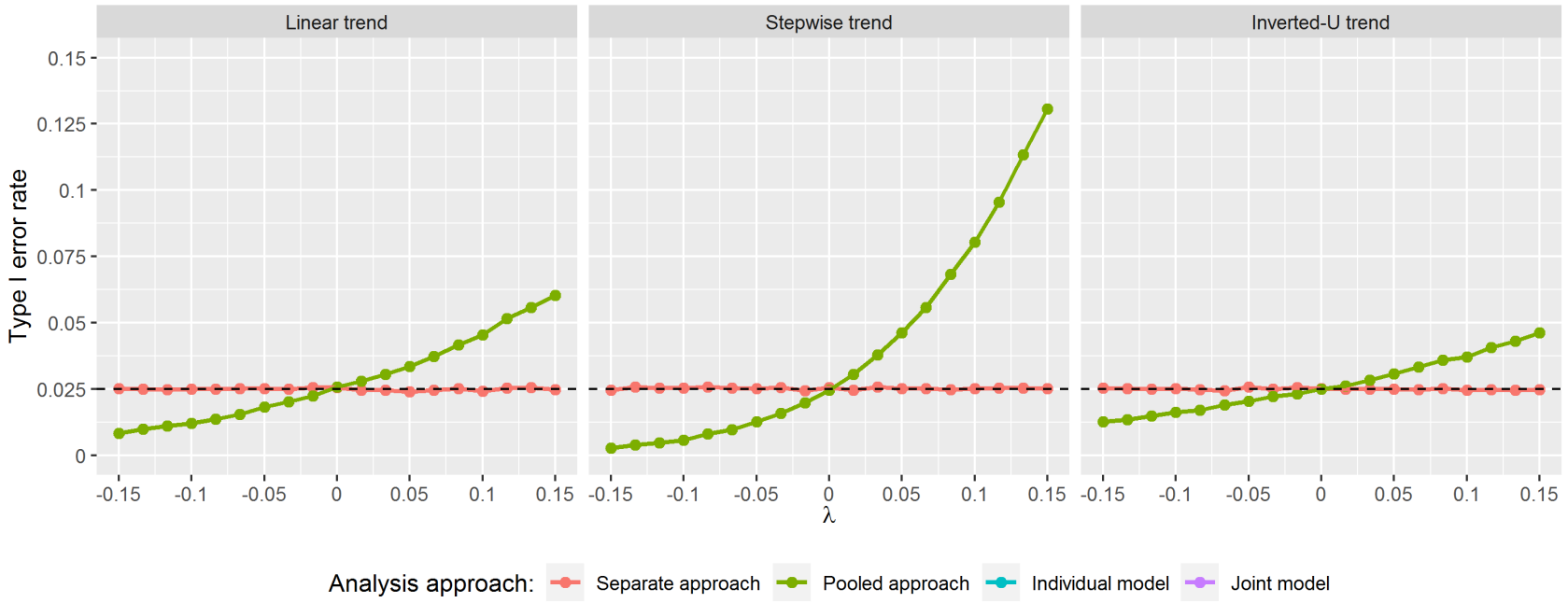

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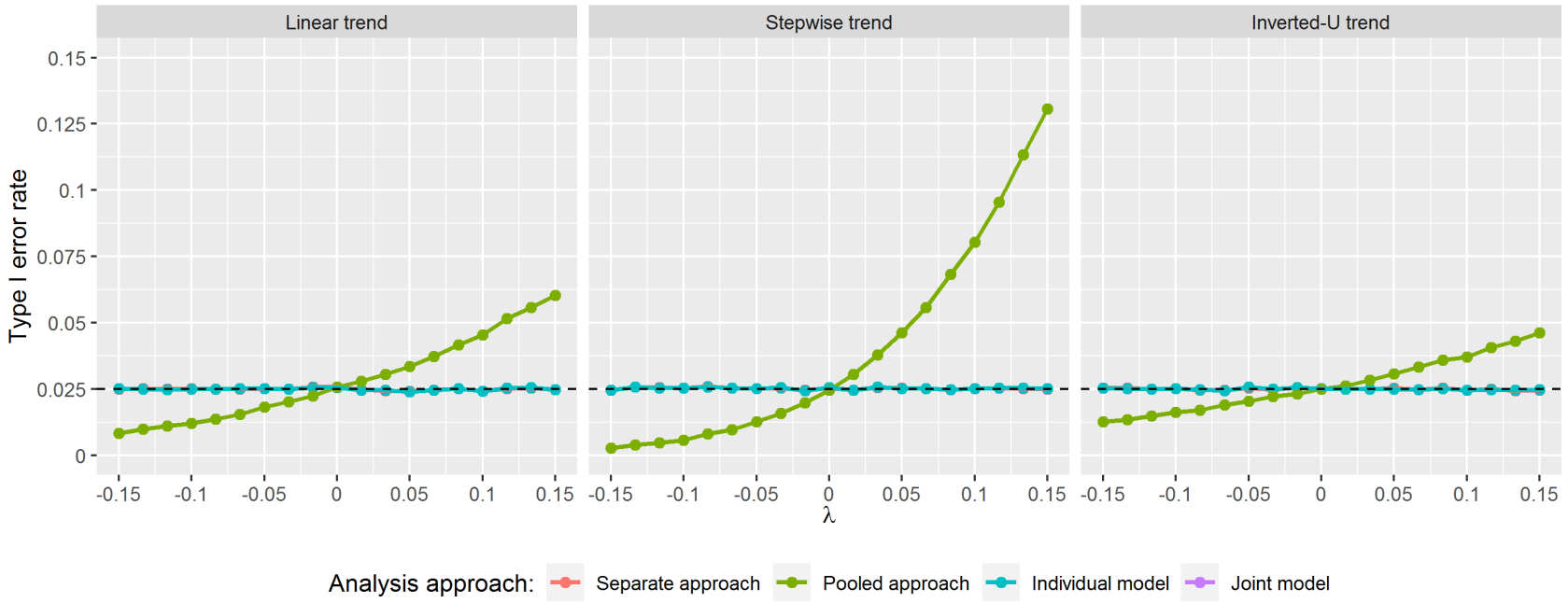

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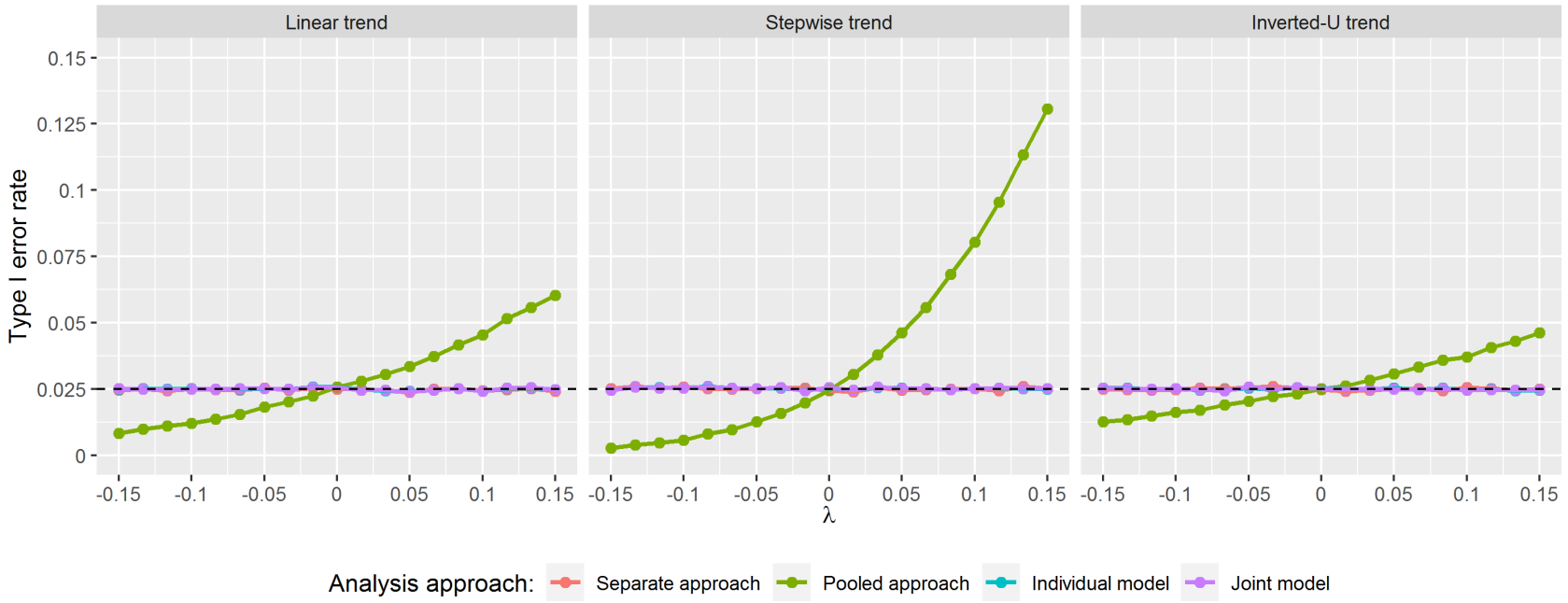

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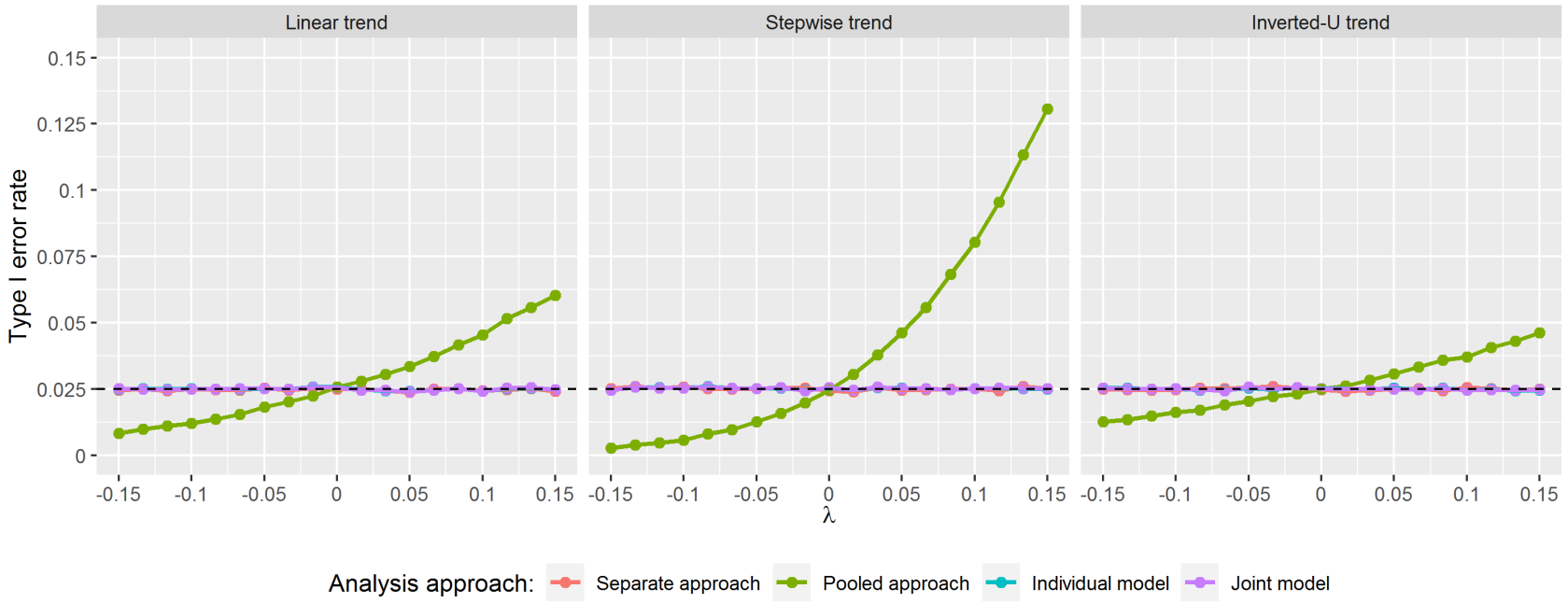

Model-based approaches:

- both control type I error rate
- both lead to an unbiased test, even if the true time trend is linear or follows another shape

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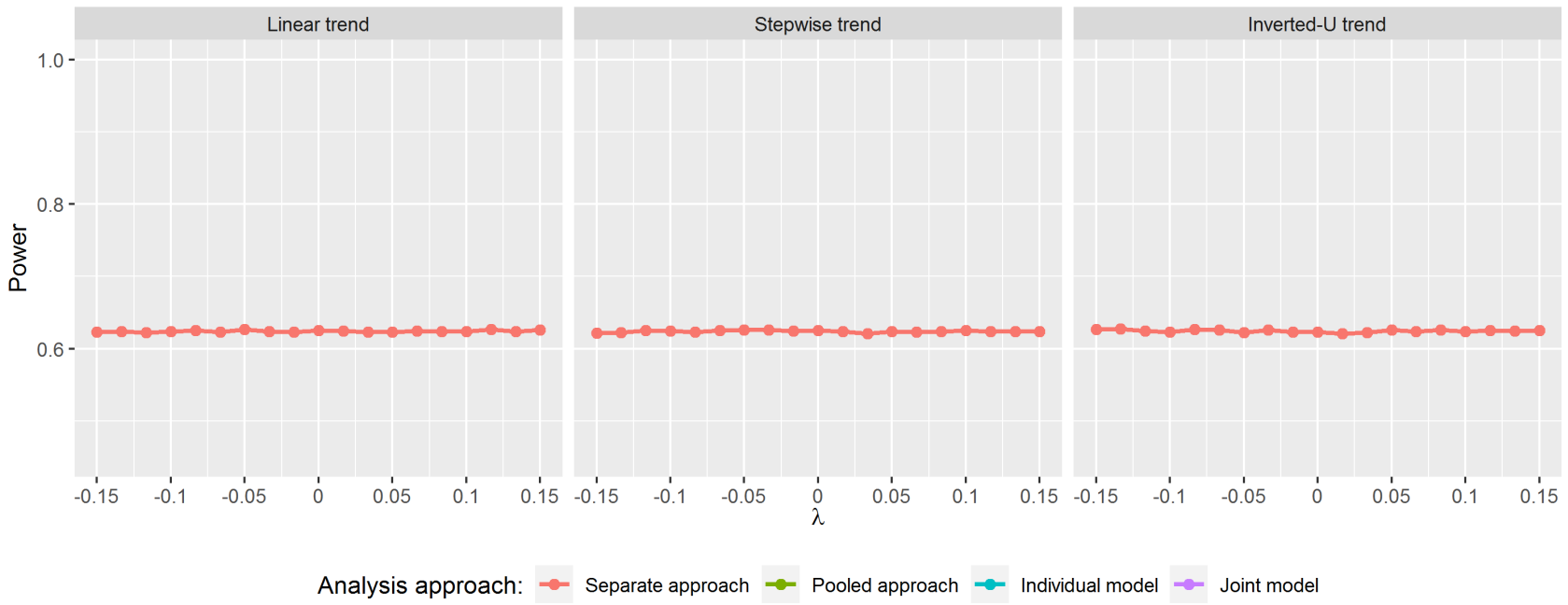
Power



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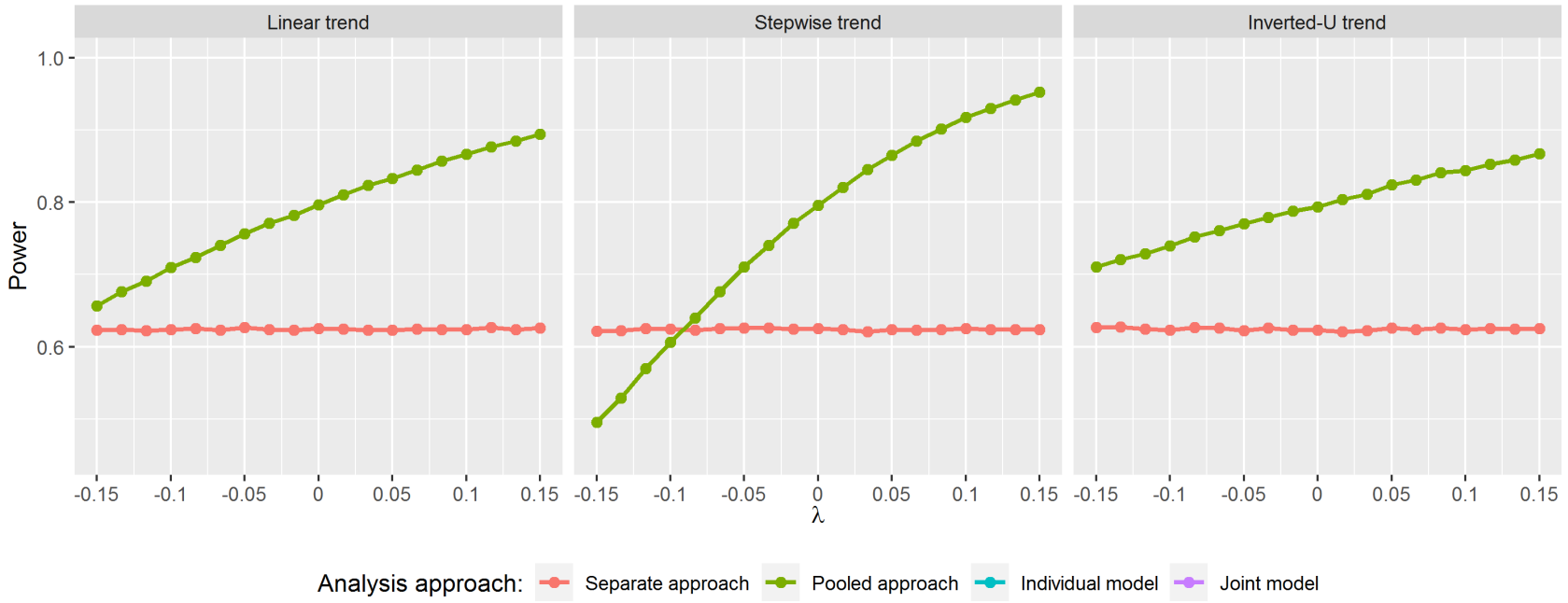

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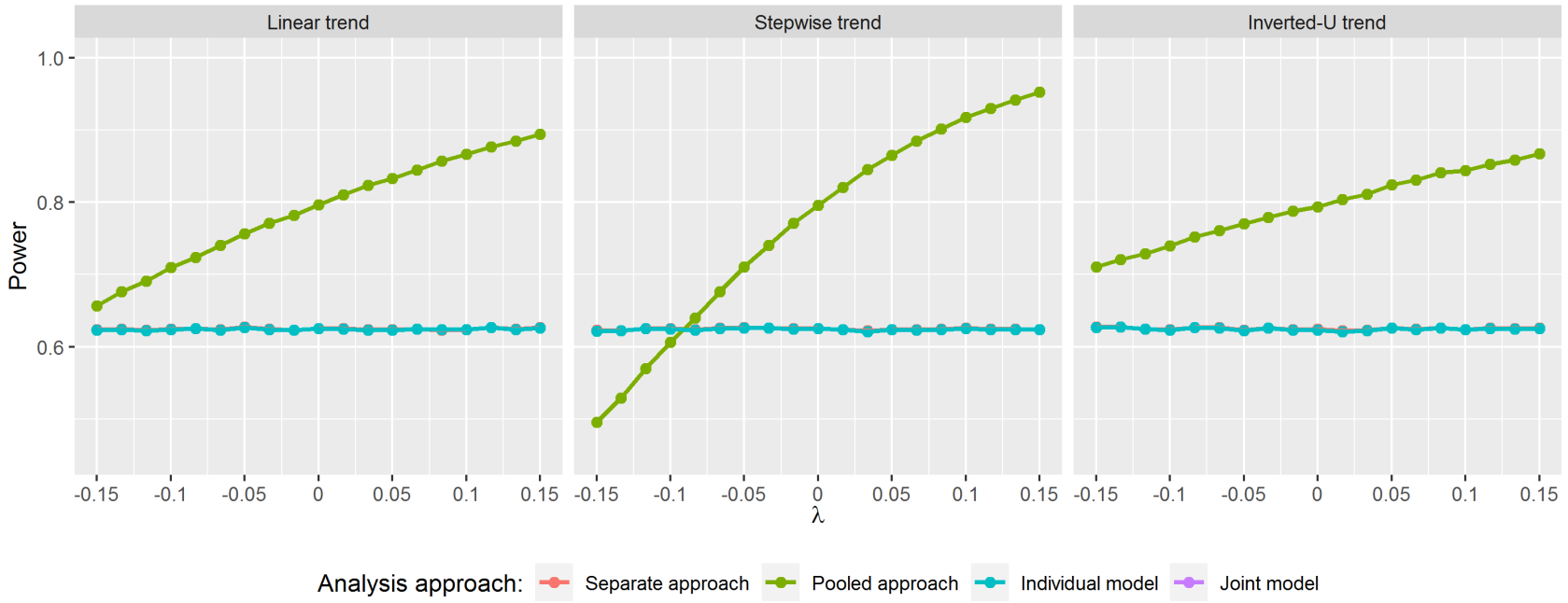

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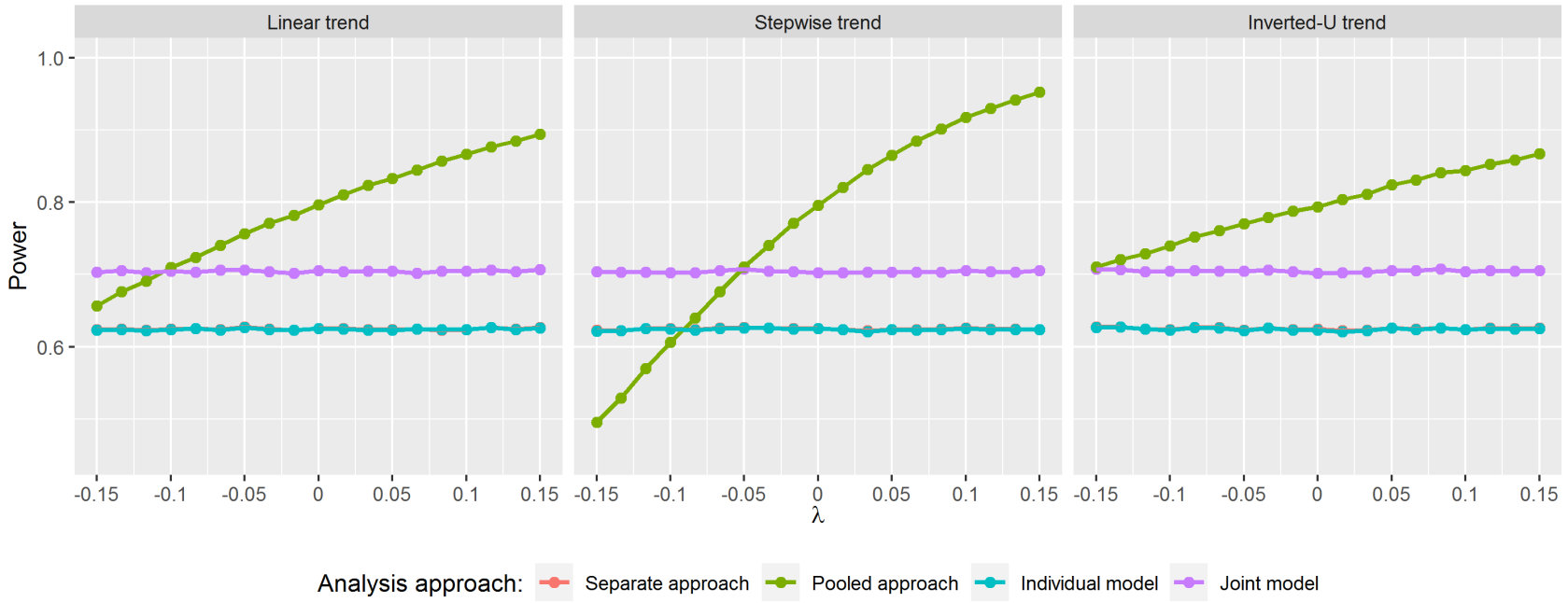

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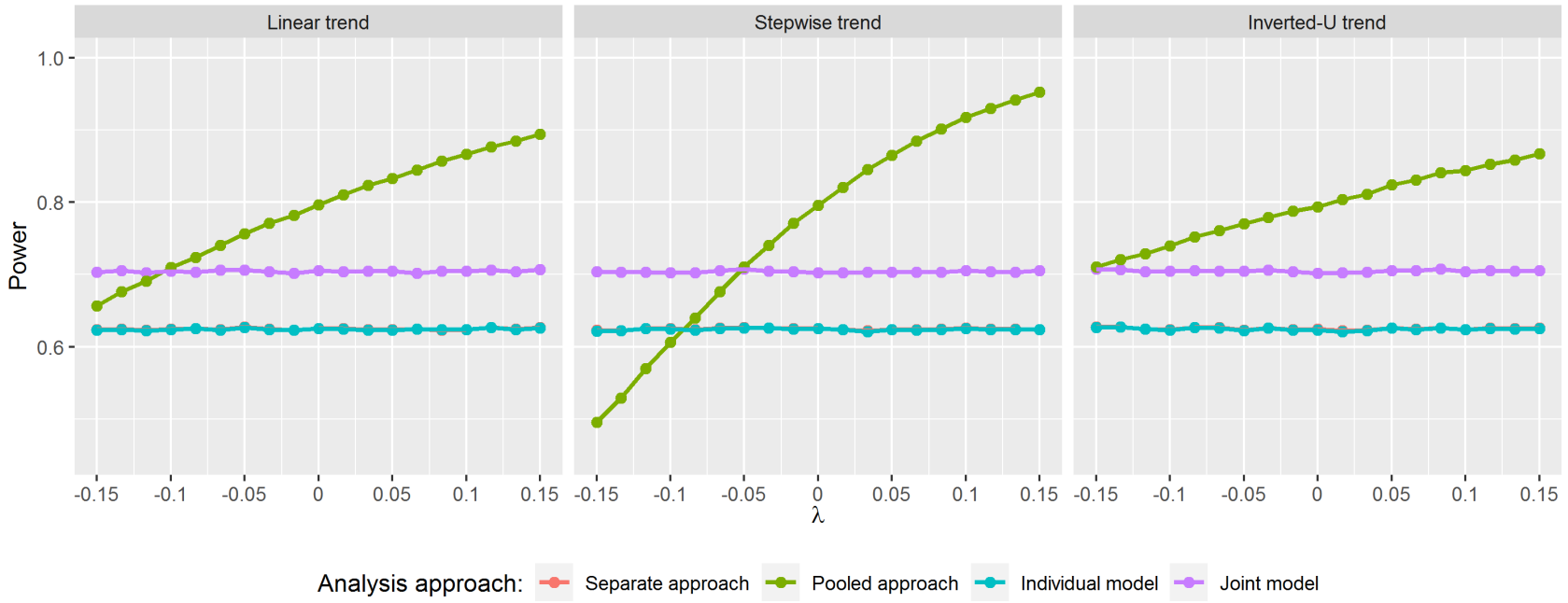
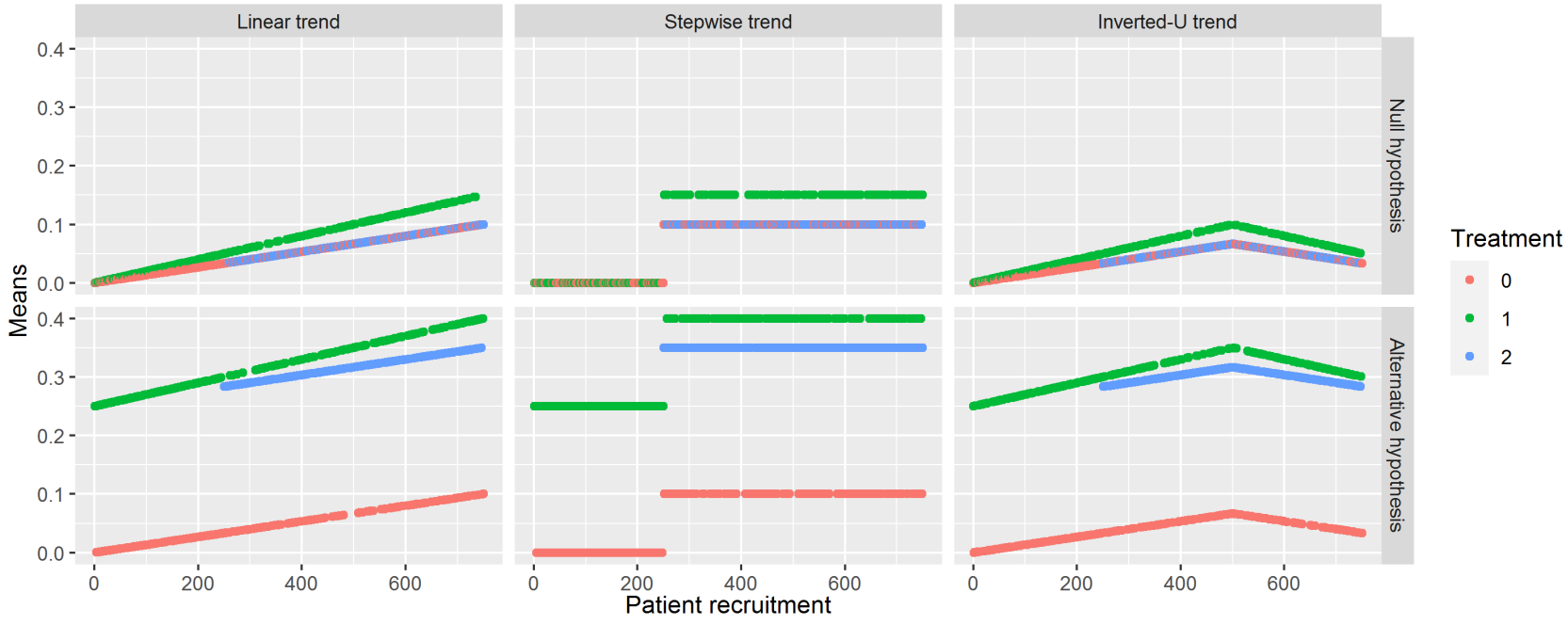


Model-based approaches:

- only in joint models the inclusion of NCC improves the power

Scenarios with different time trends



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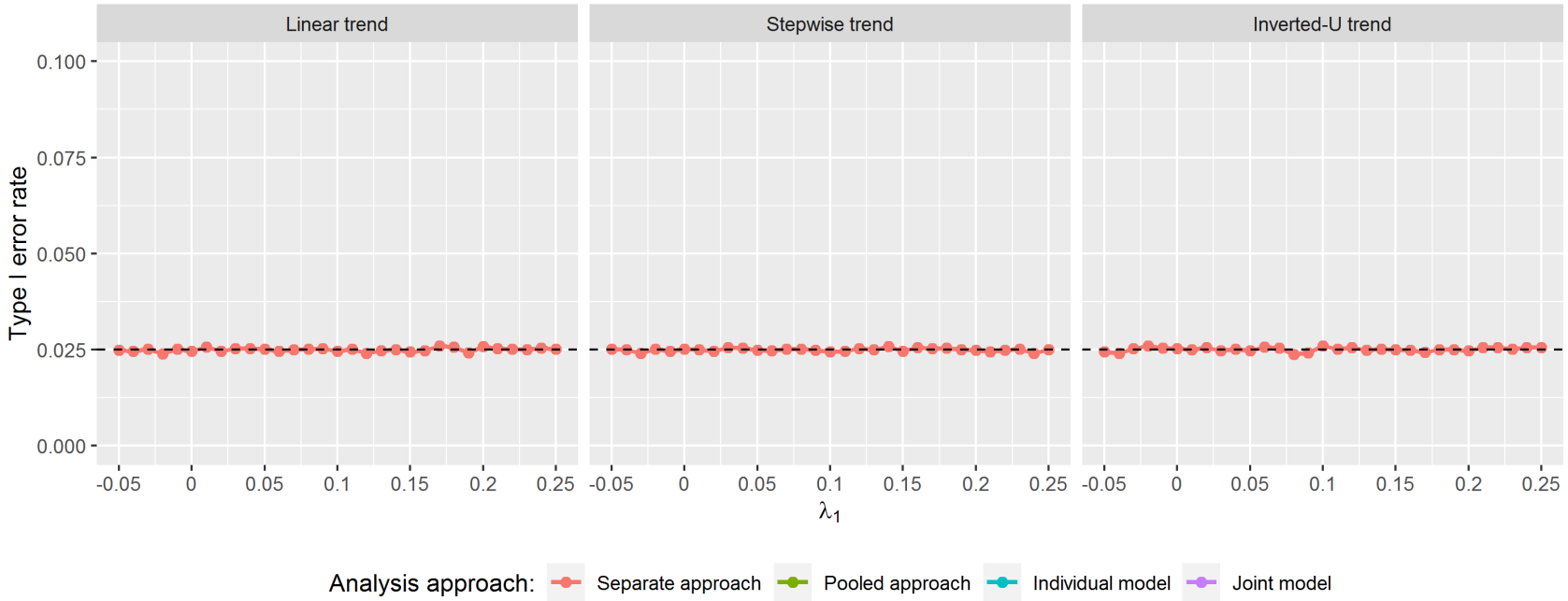

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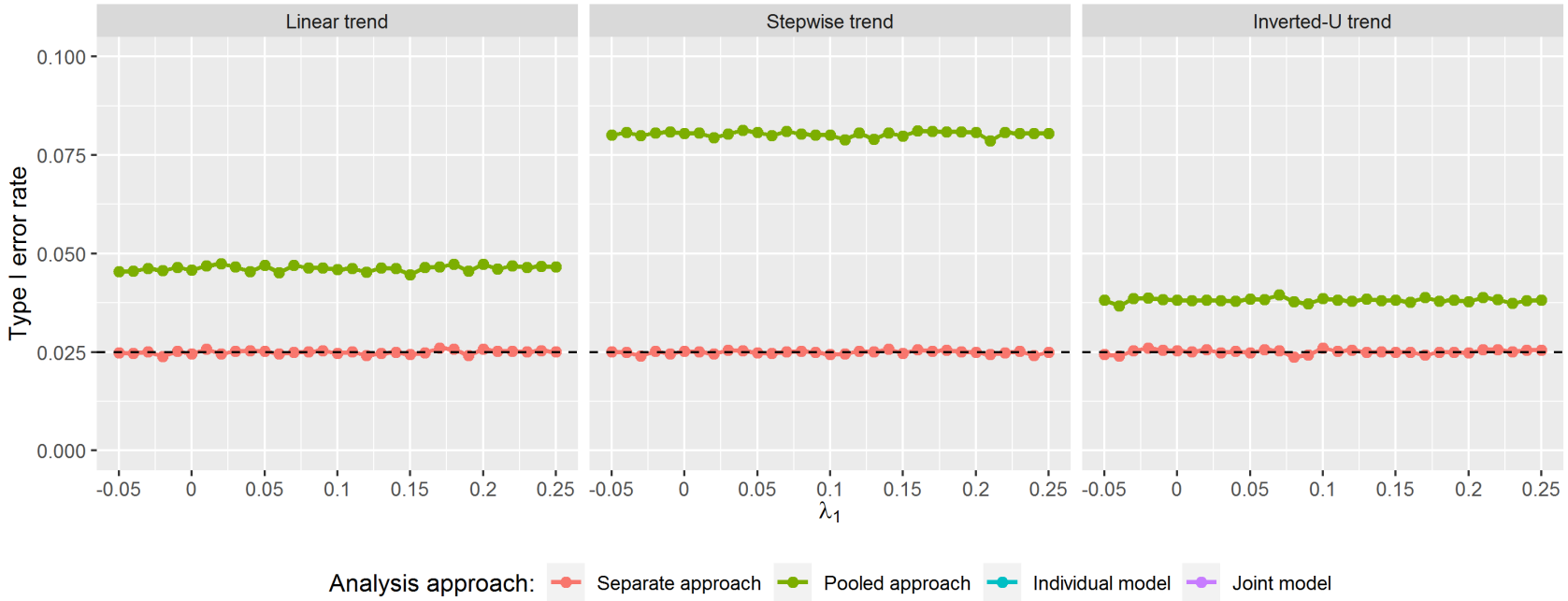

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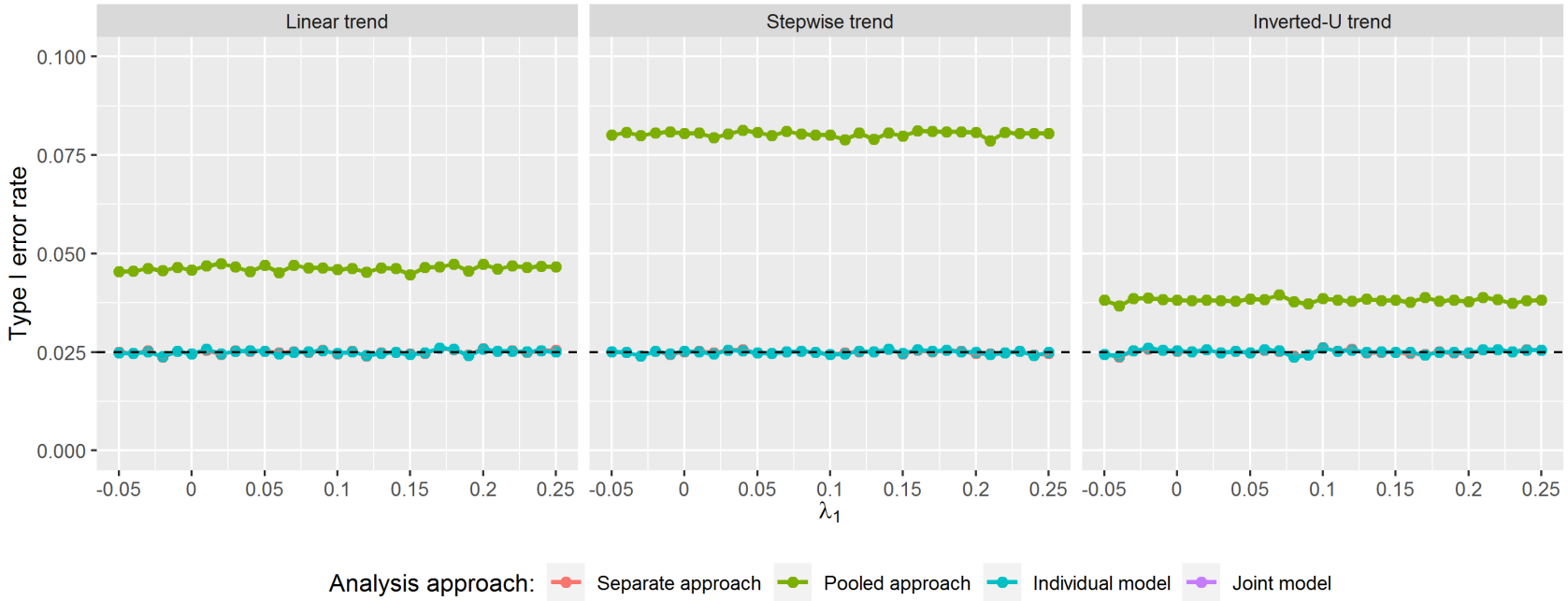

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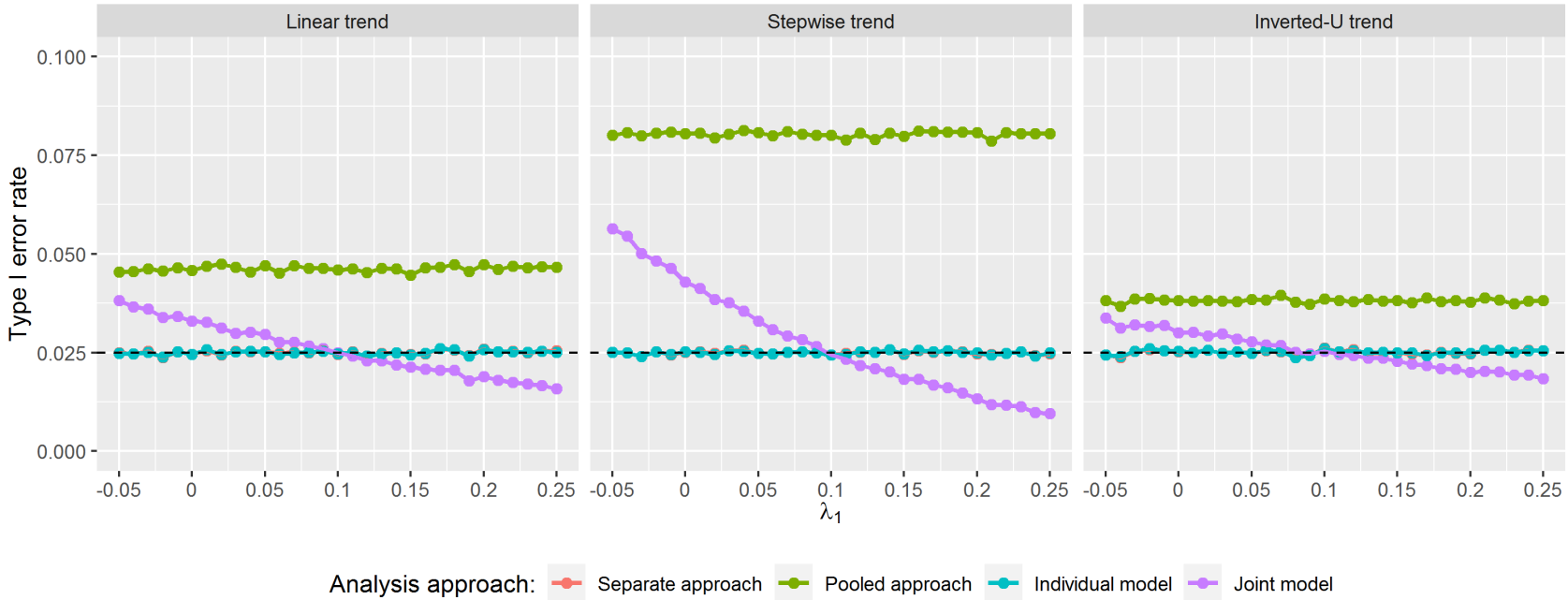
- Same time trend for treatment 2 and control arms ($\lambda_0 = \lambda_2 = 0.1$), different for arm 1



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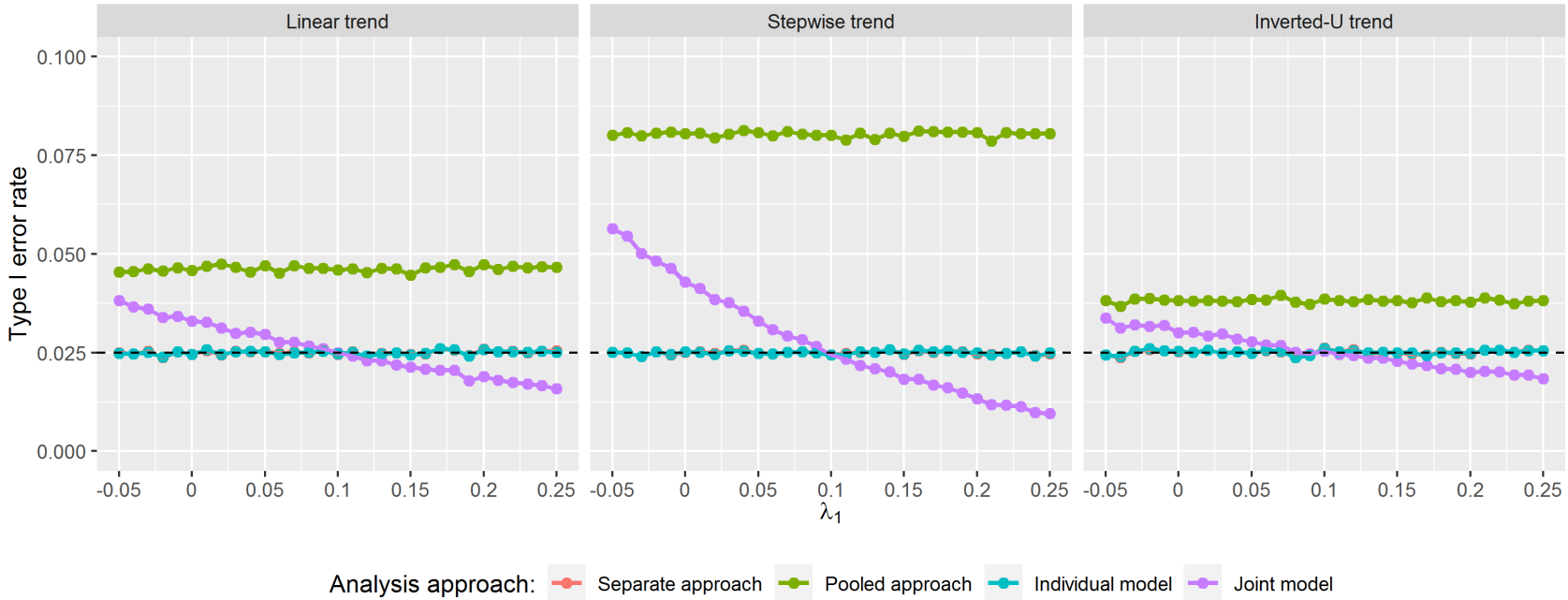

Model-based approaches:

- only individual model controls type I error rate and leads to unbiased estimator, regardless of the time trend shape

Performance for continuous endpoints with different time trends

Power

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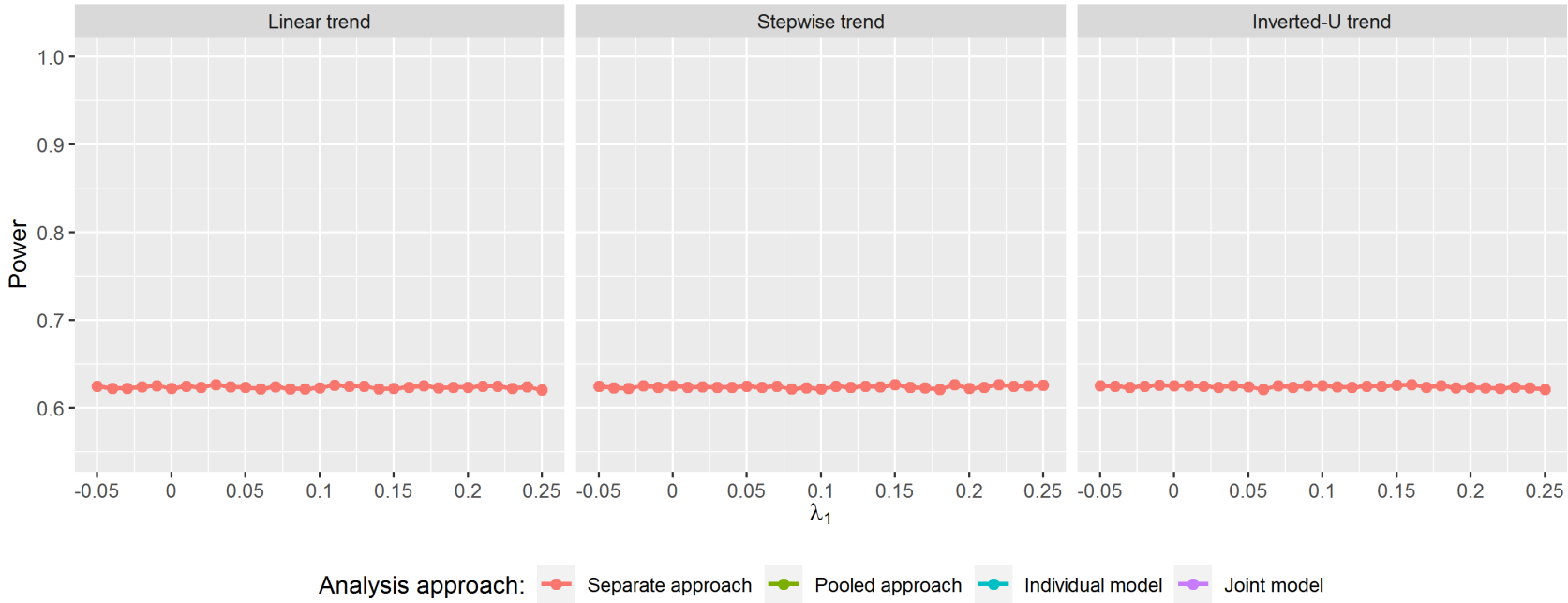

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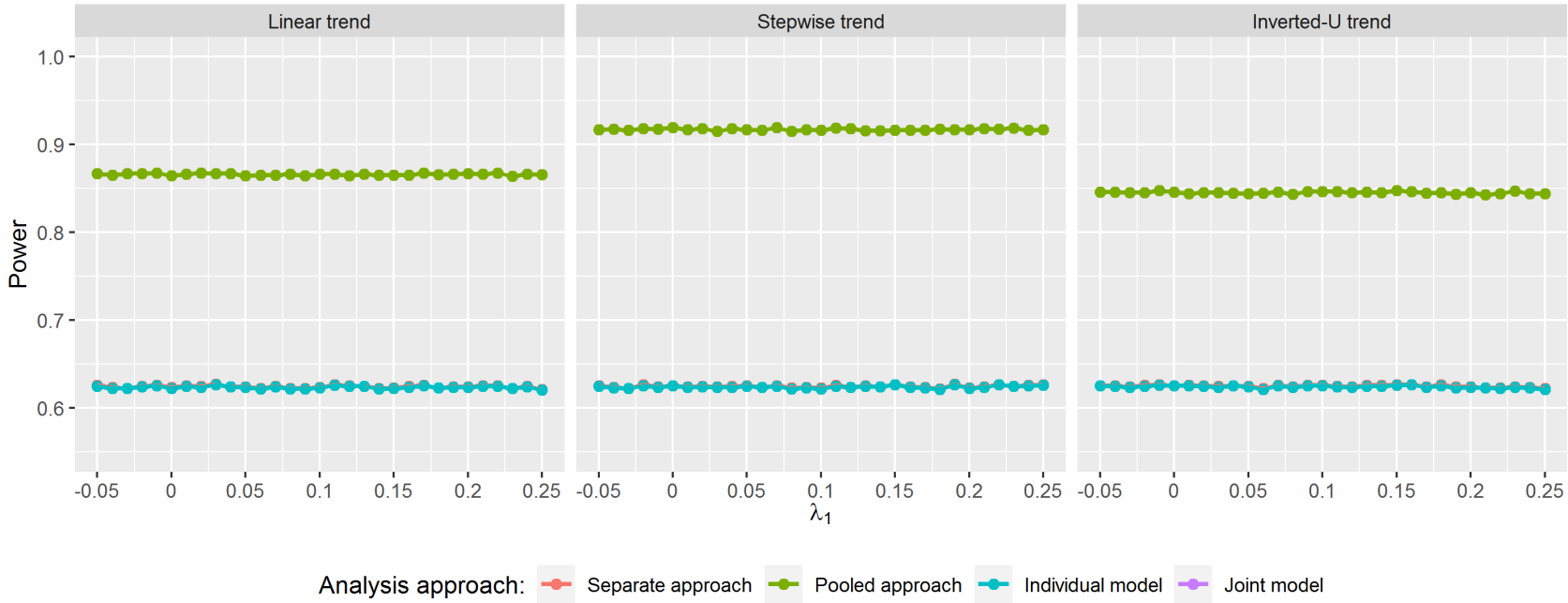

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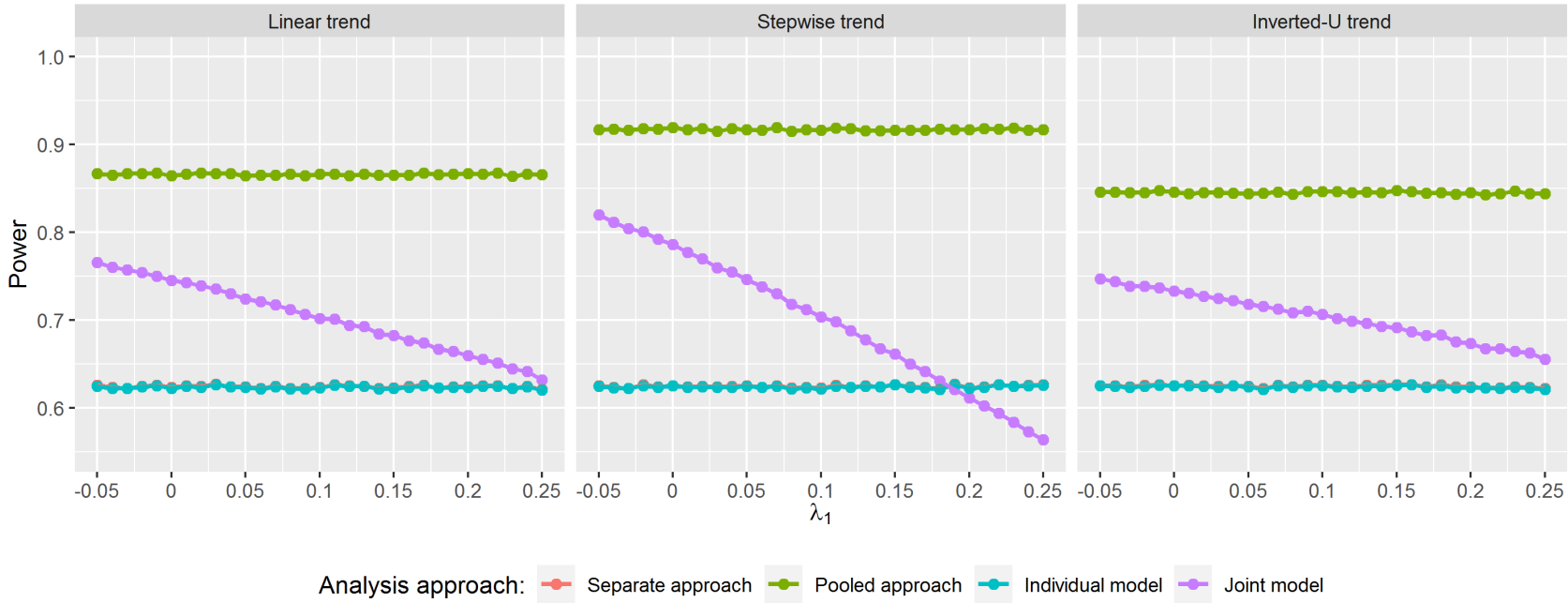

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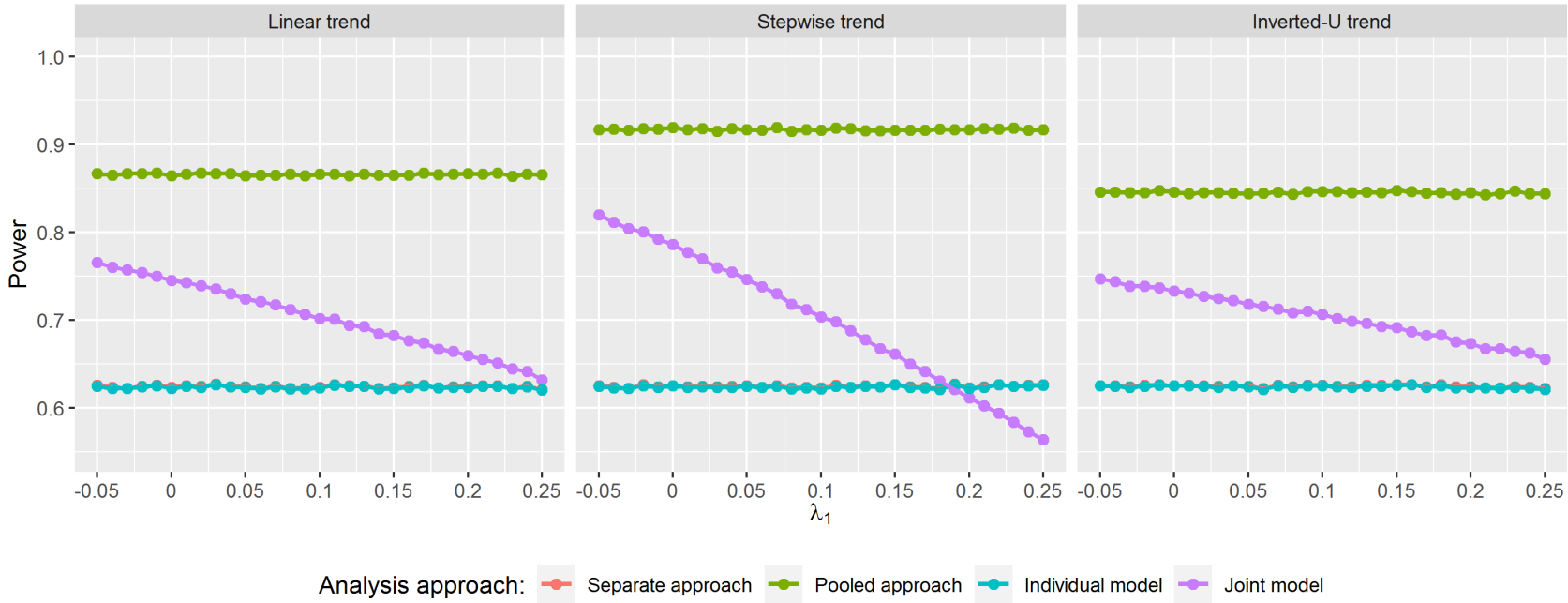

Model-based approaches:

- in joint models, the inclusion of NCC leads to power improvements, but in this case, the type I error is adversely affected

Conclusions

Use of Non-concurrent Controls in Platform Trials

- 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.
- Methods to incorporate non-concurrent controls are available. However, they rely on **specific assumptions** that have to be taken into account, e.g. the assumption of **equal time trends** in all treatment groups.
- If non-concurrent controls are used for the primary analysis, the analysis using only concurrent controls should be presented as a **sensitivity analysis**.

Other Statistical Issues in Platform Trials

- Identifying the **trial objectives**
- **Multiplicity**
  - multiple treatment groups
  - multiple endpoints
  - multiple subgroups
- Choice of **adaptation rules**
  - number and timing of interim analyses
  - stopping rules
  - timing of adding treatments
  - updating randomization ratios

Thank you very much for your attention!