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

Marta Bofill Roig, Medical University of Vienna

"On model-based time trend adjustments in platform trials with non-concurrent controls". (2021). M. Bofill Roig, P. Krotka, CF. Burman, E. Glimm, K. Hess, P. Jacko, F. Koenig, D. Magirr, P. Mesenbrink, K. Viele, and M. Posch. `https://arxiv.org/abs/2112.06574`

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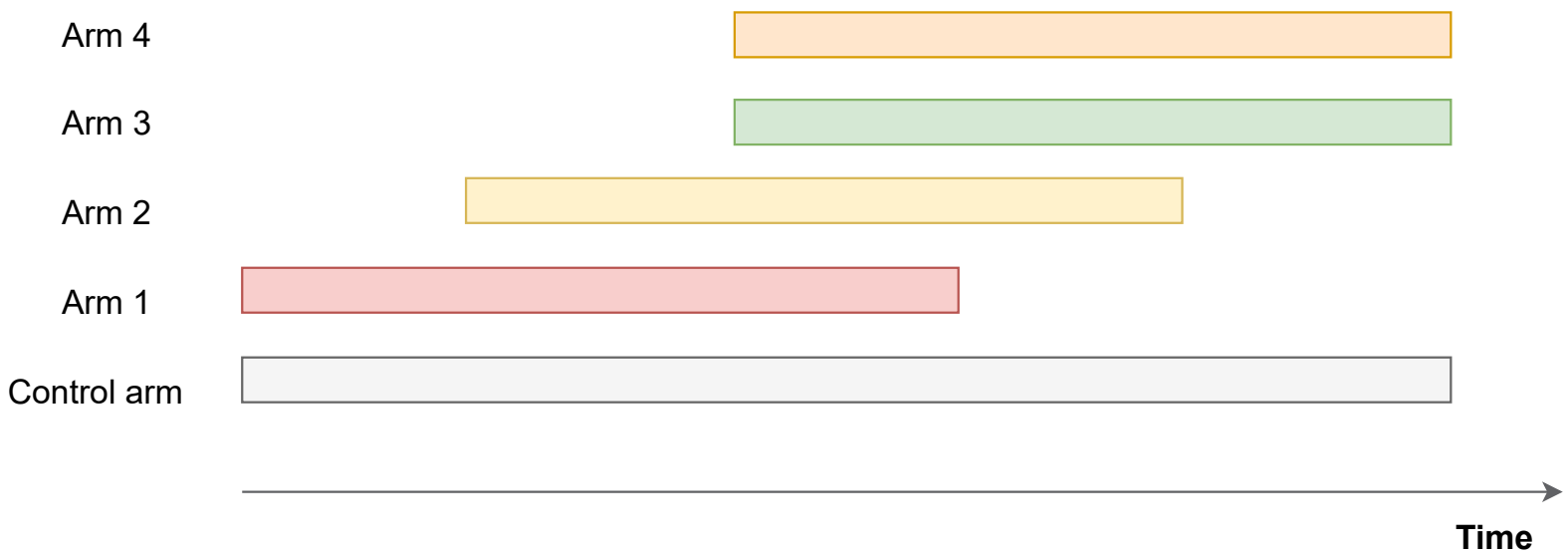
Collaborative Platform Trials

Platform trials: Multi-arm multi-stage trials that allow new experimental treatment arms to enter and leave the trial at different times.

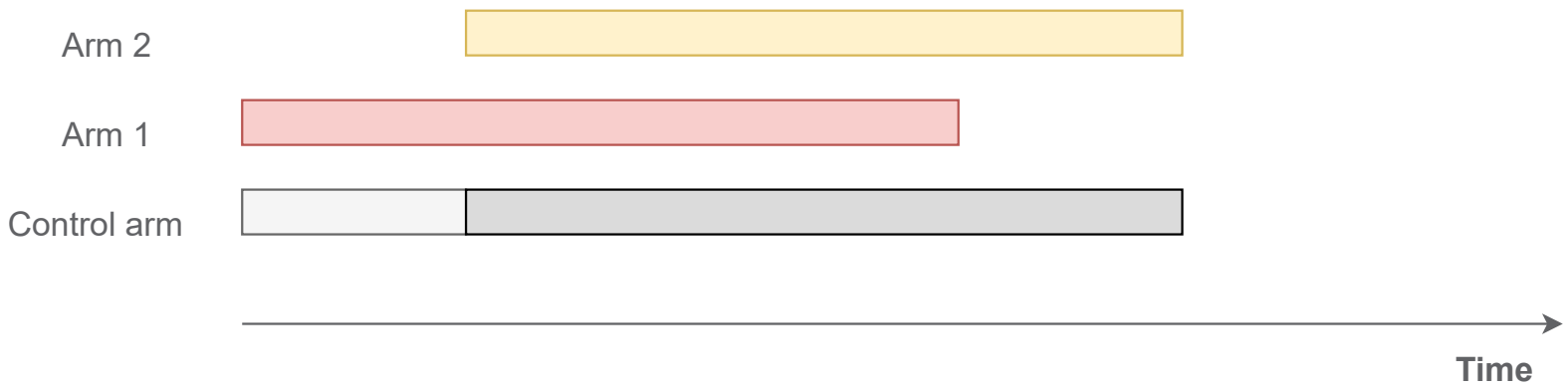
Flexible number of treatment arms and shared controls



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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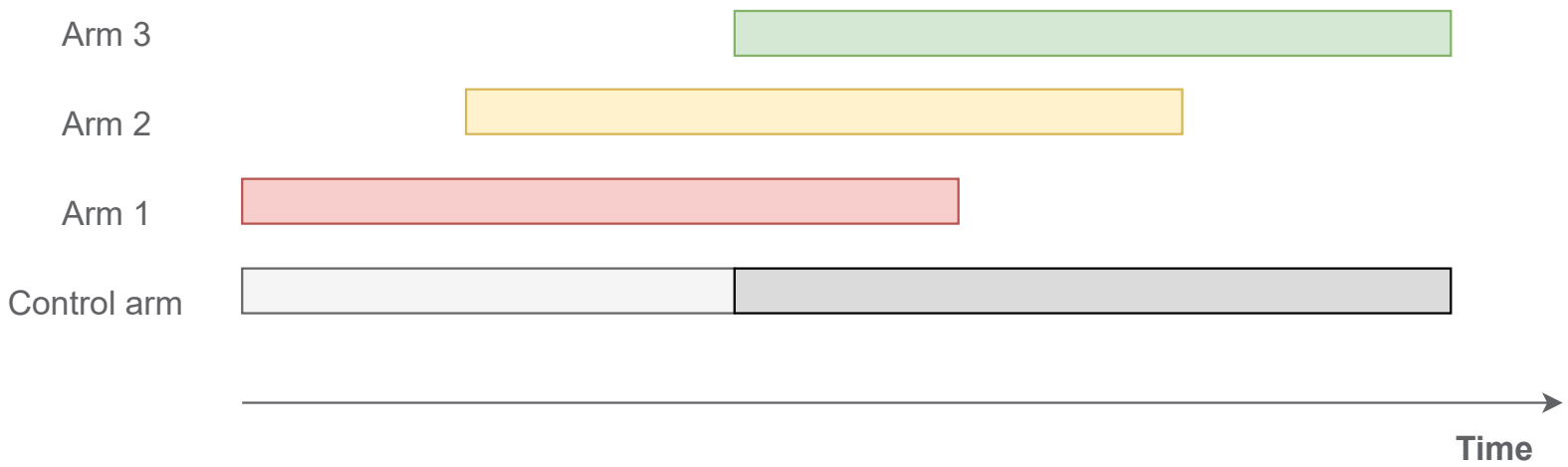


Randomized controlled trials and non-concurrent controls

Randomization

- guarantees that assigned treatment is independent of baseline characteristics;
- produces comparable groups with regard to risk factors.

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

Incorporating non-concurrent controls can improve the power of hypothesis tests and standard error of estimators but may introduce bias due to **time trends**.

Analysis methods for trials with non-concurrent controls

Separate approach: Analysis using only concurrent controls.

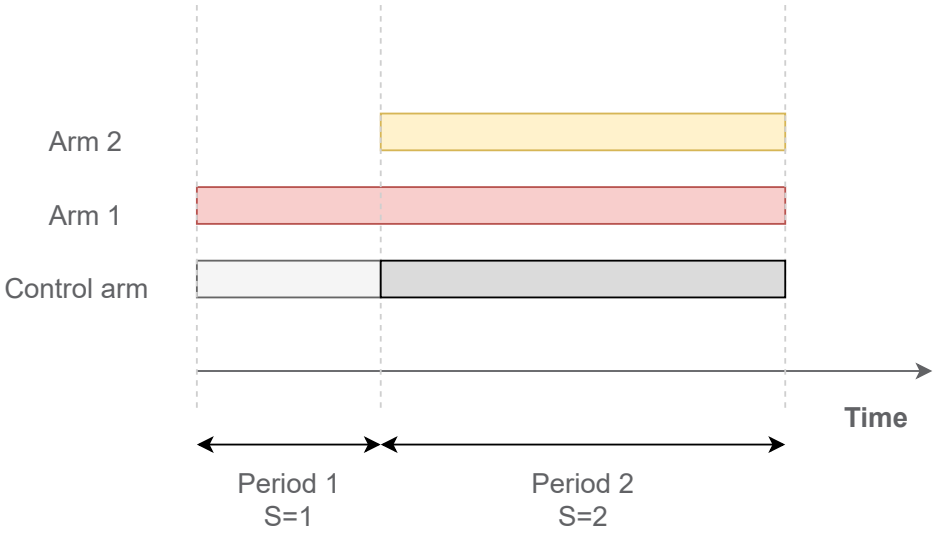
Pooled approach: Analysis using concurrent and non-concurrent controls.

Model-based approach[1]:

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.

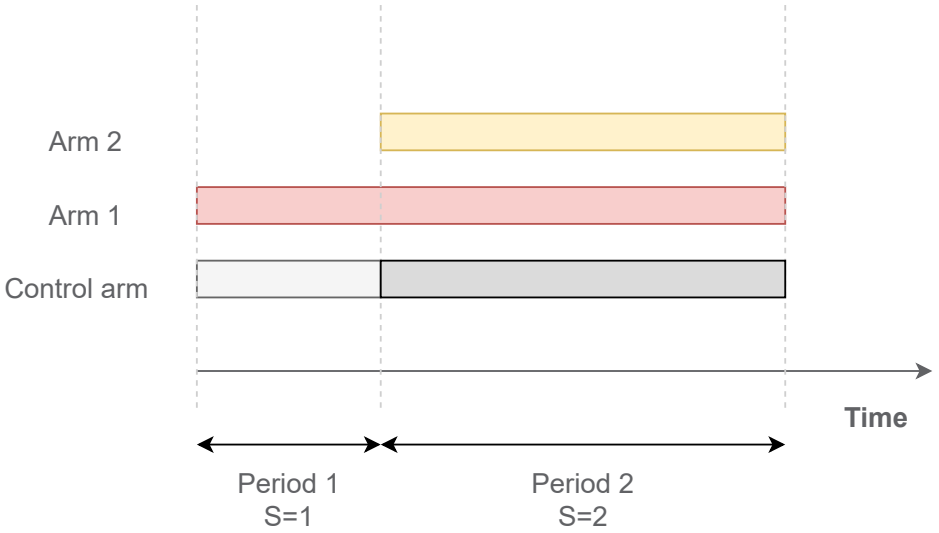
Frequentist regression methods



Hypothesis testing problem:

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

Frequentist regression methods



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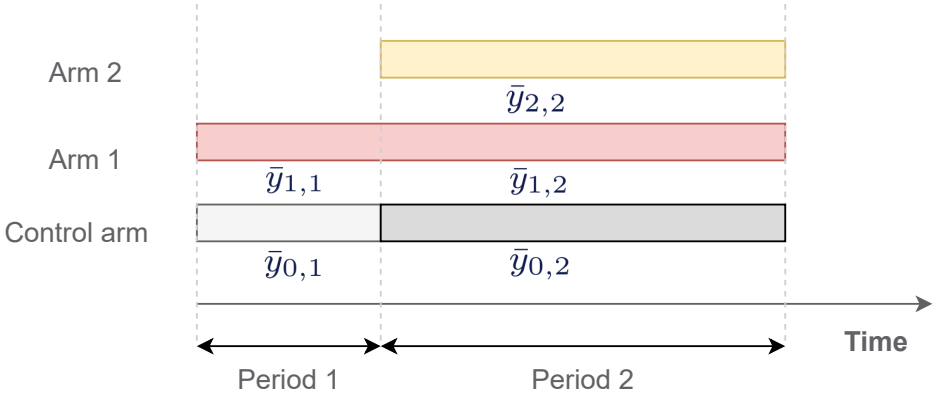
Model-based approach based on data from all treatment arms and control:

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

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



$$\varrho = \frac{\frac{1}{n_{0,2}}}{\frac{1}{n_{0,1}} + \frac{1}{n_{0,2}} + \frac{1}{n_{1,1}} + \frac{1}{n_{1,2}}}$$

Treatment **effect estimator** using separate analysis:

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

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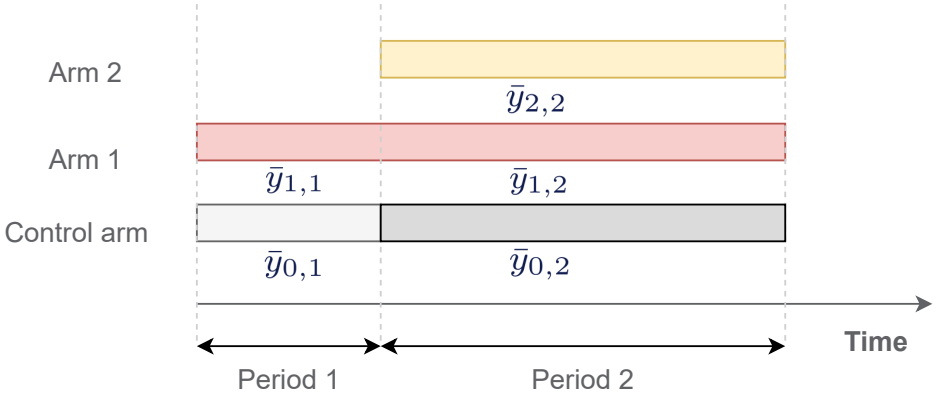

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Treatment **effect estimator** using the model-based approach:

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

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

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

Comparison of control estimate and unbiasedness of treatment effect

Reduction in variance:

$$1 - \frac{\text{Var}(\tilde{y}_{0,2})}{\text{Var}(\bar{y}_{0,2})} = \varrho,$$

$$\varrho = \frac{\frac{1}{n_{0,2}}}{\frac{1}{n_{0,1}} + \frac{1}{n_{0,2}} + \frac{1}{n_{1,1}} + \frac{1}{n_{1,2}}}$$

- Reduction in variance is increasing in the number of non-concurrent control patients, in the number of concurrent patients on arm 1, and in the number of non-concurrent patients on arm 1.
- If increasing the number of concurrent control patients but keeping the other sample sizes fixed, no reduction takes place.

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Model-based approach leads to an **unbiased treatment effect estimator** $\tilde{\theta}_2$ if the time trends in all arms are equal and additive, regardless the functional form of the time trend.

Conditions for valid inference in model-based approach

Underlying assumptions for model-based approach

(i) **Functional form of the time trends**: step-wise trends;

(ii) **Equal time trends:** The effect of time on the treatment arms is the same as in the control arms;

(iii) **Scale of the time trend**: additive in the model scale.

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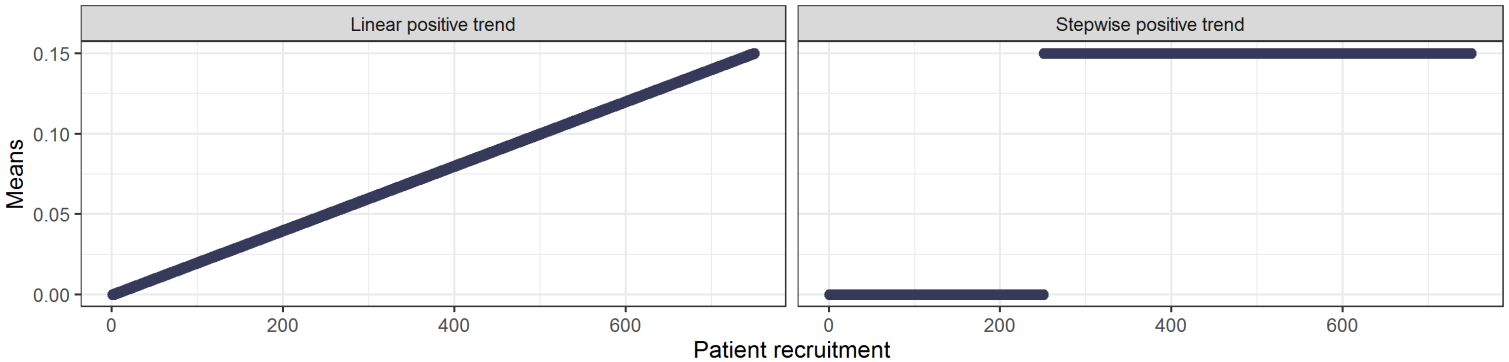
Operating characteristics:
Under which assumptions do the models lead to gain in power and type I error control?

Simulation settings:
Two experimental arms, continuous endpoints, linear and step-wise time trends

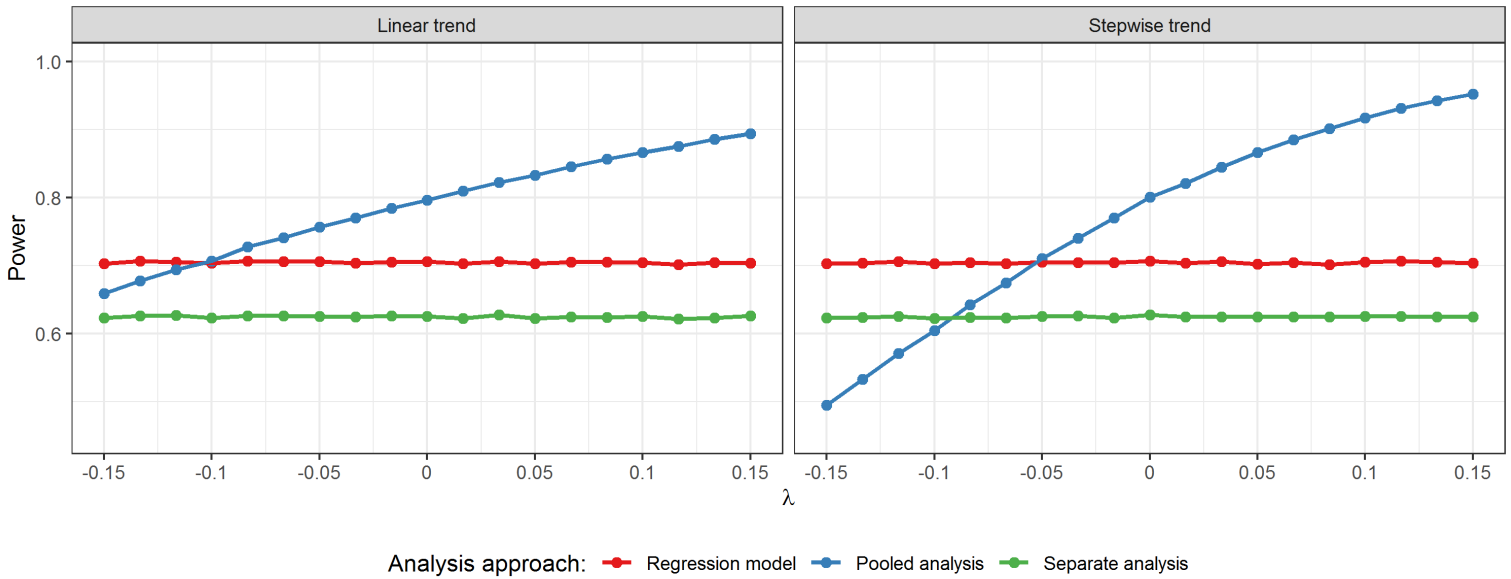


λ: strength of the time trend

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 ($\lambda = 0.15$)
- Block randomization.

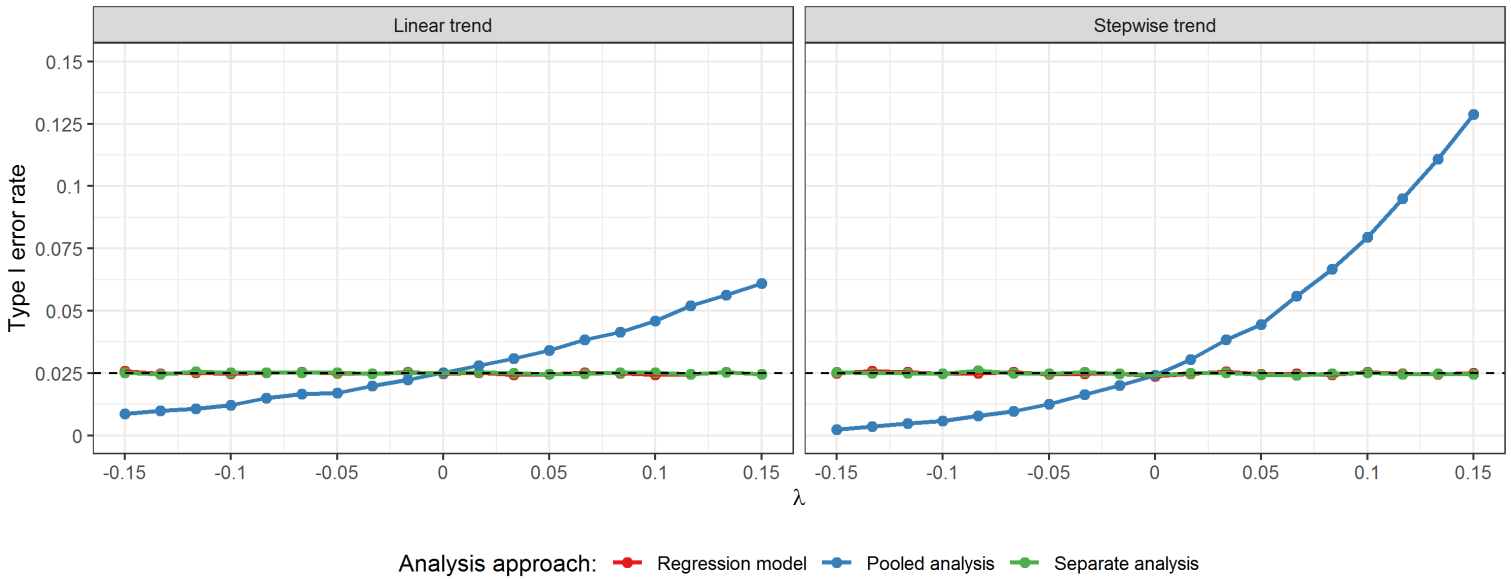


Model-based approach **improves the power** as compared to separate analysis using only CC.

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 ($\lambda = 0.15$)
- Block randomization.

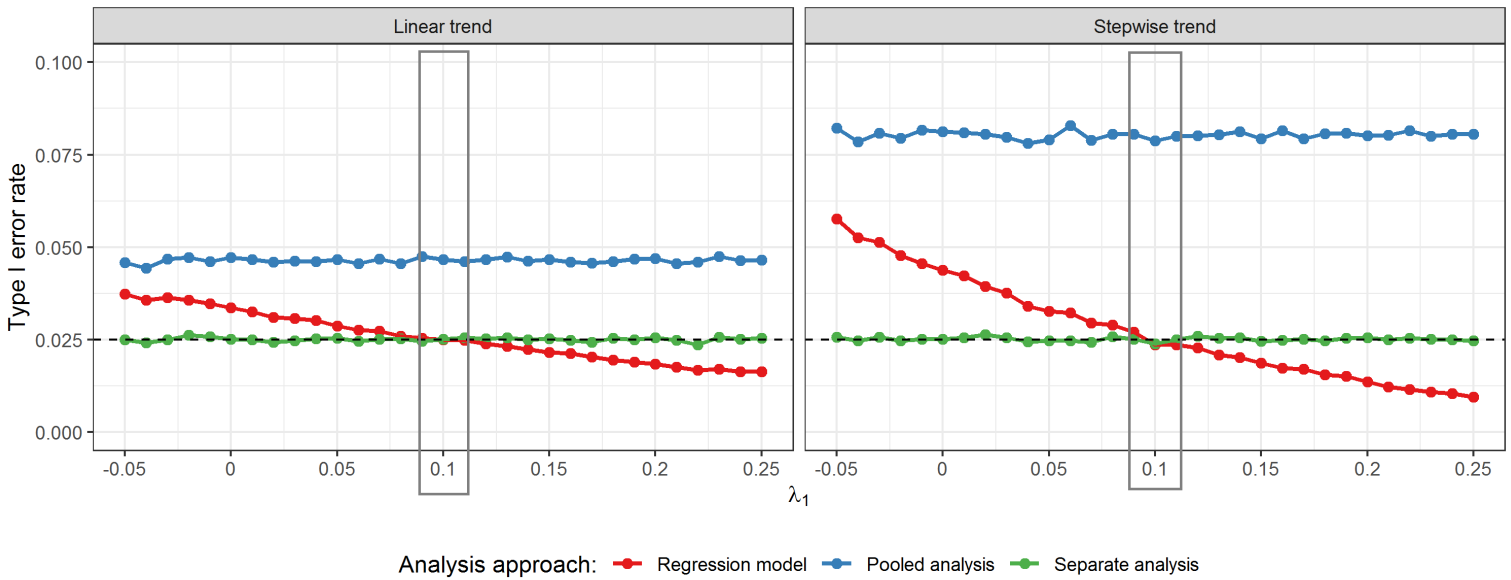


Model-based approach **controls the type I error** (T1E), even if the true trend is other than step-wise.

Type 1 error in platform trials with different time trends

Simulation settings:

- No treatment effect on arm 2 (H_0)
- Equal trend for arm 2 and control ($\lambda_0 = \lambda_2 = 0.1$) but different for arm 1 (λ_1)
- Block randomization.



Model-based approach **loses T1E control** if trends differ between arms, while **power** is **sensitive** to deviations from equal time trends and may be **reduced**.

Are different time trends across arms plausible?

Heterogeneous time trends across arms may occur in settings where treatments show an effect compared to control, but the external factors causing the time trend do not equally affect all arms.

- Vaccine trials
- Population shifts
- Additive time effects in trials with binary data

Some conclusions on the use of modeling-approach

Model-based approach using data from all treatment arms and NCC data:

- controls the T1E under the assumption of **equal time trends** in all treatment groups in the **scale of the model**,
- can substantially improve the power,
- and leads to (asymptotically)
  - unbiased estimators,
  - and unbiased hypothesis tests if block randomisation is used.

  even under misspecification of the time trend pattern.

Generalisation to more than two arms is possible and the power will further increase the more **overlap** there is between arms.

Alternative modeling-approaches

Modeling different time trends per group:

- Data of NCC do not contribute to the estimation of concurrent controls; only to the variance estimator.
- No relevant power gain.

Models for smoothly adjusting time trends:

- Choosing smooth function instead of a step function can further increase the power compared to models using data from all treatment arms.
- T1E control only guaranteed if model specification is correct.
- The more flexible the function to model the time trend, the smaller the gain in power.

Bayesian models for borrowing information about time period effects across time:

- Non-parametric estimators of the time trend.
- Again the assumption of equal time trends across groups is needed.

Methods to incorporate historical controls

Test-then-pool approach: (Pre-)Test the differences between non-concurrent with concurrent controls responses, and depending on that, do a separate analysis, otherwise a pooled analysis.

Weighted pooling: Estimating the control response by assigning a weight to the NCCs, which adjusts the importance of the NCC in the estimate.

Bayesian Robust Meta-Analytic Predictive (MAP) approach:
Using a mixture of priors for the control arm:

- Non-informative prior for the CC
- Prior based on NCC data

weighted by a parameter that controls the degree of borrowing.

Methods by downweighing the non-concurrent controls are available. However, none of them control the T1E in all scenarios.

Jiao, et al. (2019). Utilizing shared internal control arms and historical information in small-sized platform clinical trials. Journal of Biopharmaceutical Statistics

Additional aspects

Potential bias if NCC data is known before a new arm is added

Validity of statistical inference relies on pre-specification of the analysis before data becomes available.

What **if NCC data is known** when new treatments enter the platform?

- If results from completed arms are published, data from their respective controls are known. Planning the addition of new arms based on knowledge of non-concurrent data can lead to bias.
- A platform trial with a control with a random low in the outcome can be an incentive for sponsors
  - to join the platform
  - to plan an analysis including NCC
- Conversely, a platform trial with a control with a random high can be
  - a deterrent to join the platform
  - a deterrent to plan for an analysis including NCC

Conclusions

- 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 are equal in all treatment groups and the parametrization of the effect of time on the treatment effects.
- If non-concurrent controls are used for the primary analysis, the analysis using only concurrent controls should be presented as a sensitivity analysis.

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