

# NCC: An R-package for analysis and simulation of platform trials with non-concurrent controls

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# Acknowledgements

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“NCC: An R-package for analysis and simulation of platform trials with non-concurrent controls”. (2023). <https://arxiv.org/abs/2302.12634>



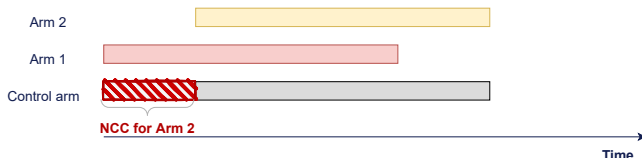
EU-PEARL (EU Patient-cEntric clinicAl tRial pLatforms) project has received funding from the Innovative Medicines Initiative (IMI) 2 Joint Undertaking (JU) under grant agreement No 853966. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA and Children's Tumor Foundation, Global Alliance for TB Drug Development non-profit organisation, Springworks Therapeutics Inc.

## 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 in the presence of time trends:

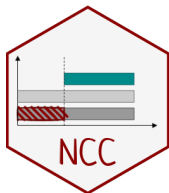
- Bias in the estimates
- Type I error rate control



Modelling  
approaches

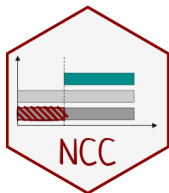
## Aims:

- Simulate platform trials with shared controls in the presence of time trends
- Analyze data using various methods for incorporating NCC
- Perform simulation studies to evaluate and compare the performance of the methods



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## Data generation:

- Functions to simulate a platform trial with continuous or binary outcome

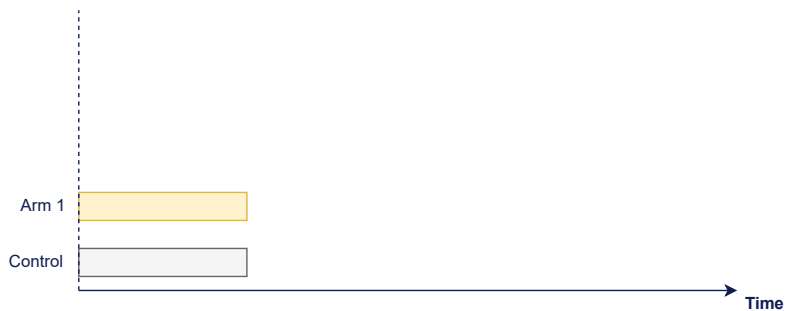
## Analysis approaches:

- Regression models with fixed effects
- Time Machine model
- MAP prior approach
- Pooled and separate analysis

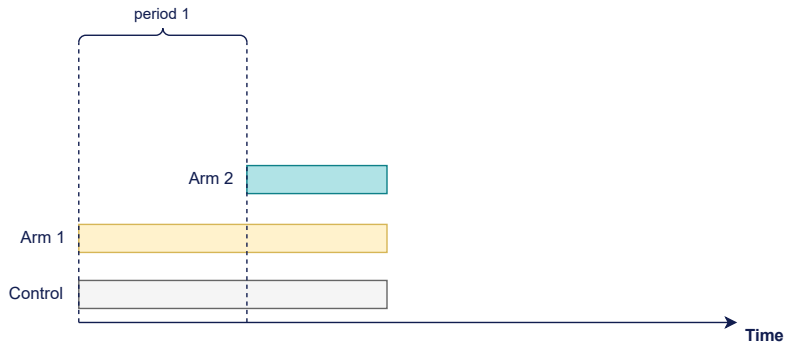
## Wrapper functions:

- Functions to run simulations in parallel and evaluate the operating characteristics of the implemented methods

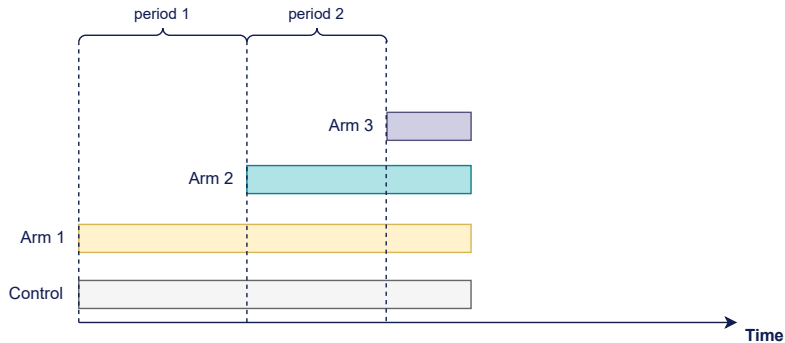
# Motivating trial design



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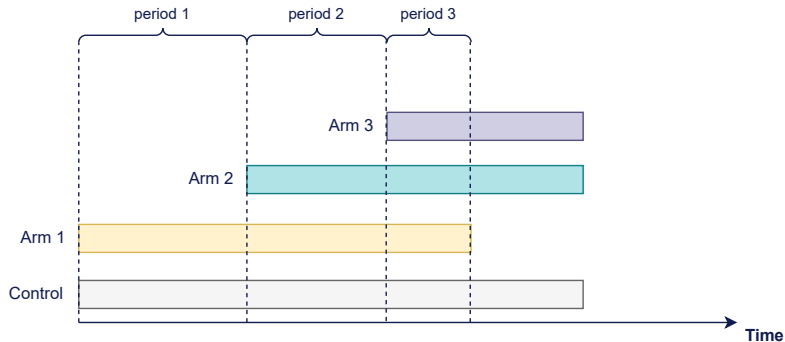


# Motivating trial design

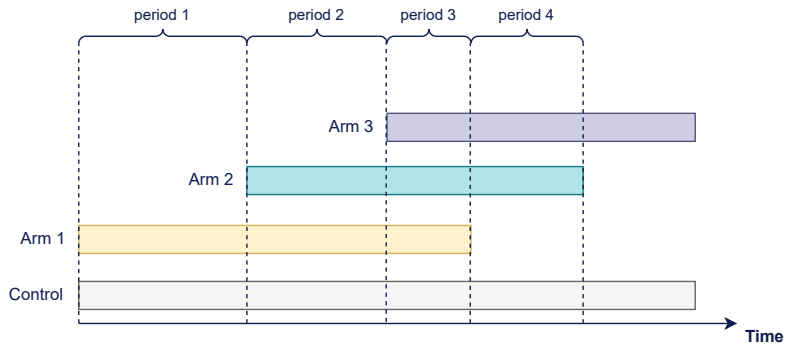




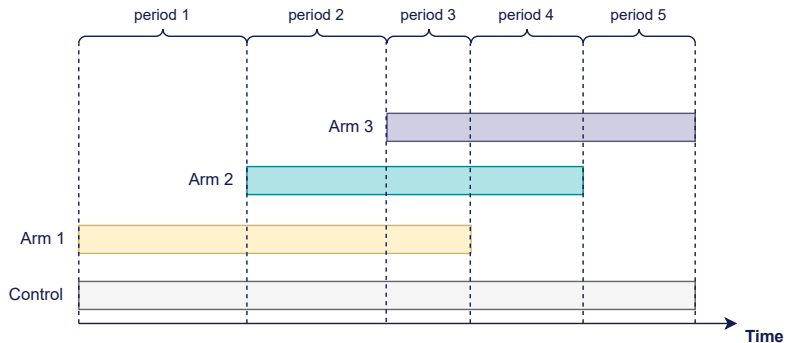
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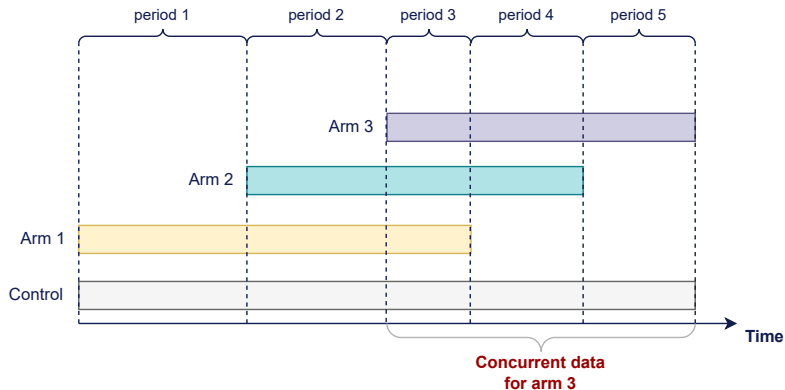


**Hypothesis testing problem:**

$$H_0 : \theta_3 = 0$$

$$H_1 : \theta_3 > 0$$

# Motivating trial design

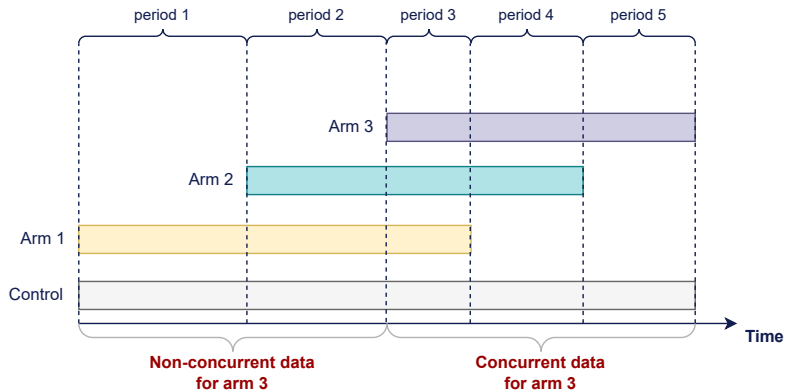


**Hypothesis testing problem:**

$$H_0 : \theta_3 = 0$$

$$H_1 : \theta_3 > 0$$

# Motivating trial design



**Hypothesis testing problem:**

$$H_0 : \theta_3 = 0$$

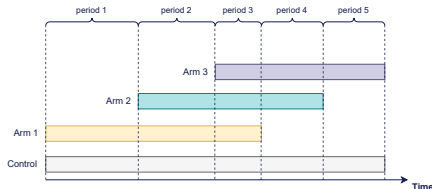
$$H_1 : \theta_3 > 0$$

# How to simulate data from a platform trial using the NCC package

## Simulating a platform trial with binary endpoints:

```
datasim_bin(num_arms = 3, n_arm = 250, d = c(0, 250, 500),  
            p0 = 0.5, OR = c(1.65, 1.65, 1.65),  
            trend = "linear", lambda = c(0.15, 0.15, 0.15, 0.15))
```

- Platform trial with 3 experimental treatment arms in total
- Sample sizes of 250 in each experimental treatment arm
- Arms 2 and 3 entering after 250 and 500 patients have been recruited
- Control response at the start of the trial of 0.5 and odds ratios of 1.65 in each experimental treatment arm
- Block randomization with 1 : 1 : ... : 1 allocation rates is used to assign patients to the active arms

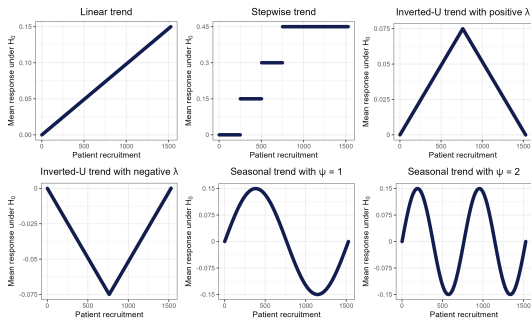


# How to simulate data from a platform trial using the NCC package

## Simulating a platform trial with binary endpoints:

```
datasim_bin(num_arms = 3, n_arm = 250, d = c(0, 250, 500),  
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            trend = "linear", lambda = c(0.15, 0.15, 0.15, 0.15))
```

- Linear time trend of strength 0.15 in each arm



Analogous function for continuous endpoints: `datasim_cont()`

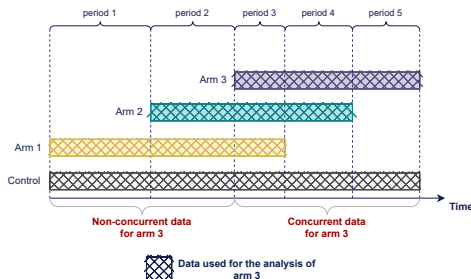
# Modelling approaches – Frequentist model-based approach

Adjusts for time trends by adding time as a covariate into the regression model<sup>1</sup>:

$$g(E(y_j)) = \eta_0 + \sum_{k=1}^3 \theta_k \cdot I(k_j = k) + \sum_{s=2}^5 \tau_s \cdot I(s_j = s)$$

## Notation:

- $y_j$  ... response for patient  $j$
- $\eta_0$  ... control response in the first period
- $k_j$  ... treatment arm patient  $j$  is allocated in
- $s_j$  ... period patient  $j$  was recruited in
- $\theta_k$  ... treatment effect of treatment arm  $k$
- $\tau_s$  ... time effect in period  $s$



<sup>1</sup>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.



## Implementation in the NCC package:

```
fixmodel_bin(data = trial_data, arm = 3, alpha = 0.025)
```

### Input:

- Data frame with trial data
- Arm to perform inference on
- Significance level

treatment	period	response
0	1	0
1	1	1
0	1	1
...	...	...

## Implementation in the NCC package:

```
fixmodel_bin(data = trial_data, arm = 3, alpha = 0.025)
```

### Input:

- Data frame with trial data
- Arm to perform inference on
- Significance level

treatment	period	response
0	1	0
1	1	1
0	1	1
...	...	...

### Output:

- One-sided p-value
- Estimated treatment effect in terms of the log-odds ratio
- 95% confidence interval for the log-odds ratio
- Indicator of whether the null hypothesis was rejected or not
- Fitted model

## Analogous function for continuous endpoints:

```
fixmodel_cont(data = trial_data, arm = 3, alpha = 0.025)
```

# Modelling approaches – Bayesian Time Machine

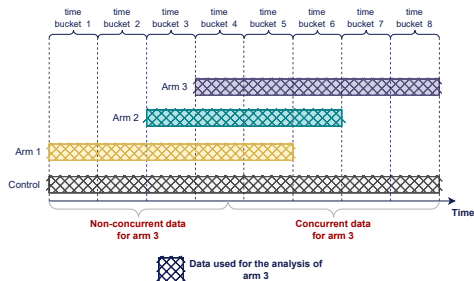
Divides the trial duration into time buckets indexed by  $c$  and smooths the control response over time using a second-order Bayesian normal dynamic linear model<sup>2</sup>:

$$g(E(y_j)) = \eta_0 + \theta_{k_j} + \alpha_{c_j}$$

where  $\alpha_{c_j}$  models the drift over time, considering  $\alpha_1 = 0$  and

$$\alpha_2 \sim \mathcal{N}(0, 1/\tau) \quad \text{and} \quad \alpha_c \sim \mathcal{N}(2\alpha_{c-1} - \alpha_{c-2}, 1/\tau)$$

- Normal priors on the control response and treatment effects
- Gamma prior on  $\tau$
- Closer time buckets are assumed to be more similar



<sup>2</sup>Saville, B. R., Berry, D. A., et al. (2022). The Bayesian Time Machine: Accounting for Temporal Drift in Multi-arm Platform Trials. *Clinical Trials*.

## Implementation in the NCC package:

```
timemachine_bin(data = trial_data, arm = 3, alpha = 0.025,  
               bucket_size = 25, prec_theta = 0.001, prec_eta = 0.001,  
               tau_a = 0.1, tau_b = 0.01)
```

### Input:

- Data frame with trial data
- Arm to perform inference on
- Decision boundary
- Bucket size
- Parameters for prior distributions

treatment	period	response
0	1	0
1	1	1
0	1	1
...	...	...

## Implementation in the NCC package:

```
timemachine_bin(data = trial_data, arm = 3, alpha = 0.025,  
               bucket_size = 25, prec_theta = 0.001, prec_eta = 0.001,  
               tau_a = 0.1, tau_b = 0.01)
```

### Input:

- Data frame with trial data
- Arm to perform inference on
- Decision boundary
- Bucket size
- Parameters for prior distributions

treatment	period	response
0	1	0
1	1	1
0	1	1
...	...	...

### Output:

- Posterior probability that the log-odds ratio is less than zero
- Estimated treatment effect in terms of the posterior mean of log-odds ratio
- 95% credible interval for the log-odds ratio
- Indicator of whether the null hypothesis was rejected or not

## Analogous function for continuous endpoints:

```
timemachine_cont(data = trial_data, arm = 3, alpha = 0.025, ...)
```

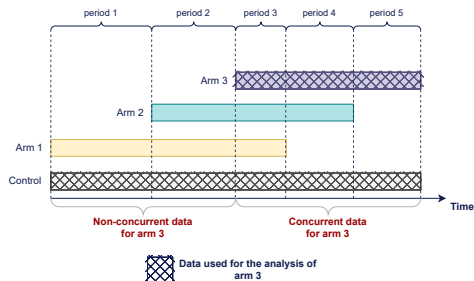
## Downweighting approaches – Meta-analytic-predictive (MAP) prior approach

Derives a prior distribution for the control response in the concurrent periods from the non-concurrent control data<sup>3</sup>.

**MAP prior:**  $p_{MAP}(\eta_{CC})$  for the concurrent control response derived as a posterior distribution of the response in the NCC data

**Robustified MAP:** Mixture of the MAP prior and a non-informative prior

- Normal prior on the control response in non-concurrent periods
- The MAP approach takes into account the heterogeneity of the control data from different periods to decide the amount of borrowing



<sup>3</sup>Schmidli, H., et al. (2014). Robust meta-analytic-predictive priors in clinical trials with historical control information. *Biometrics*.

## Downweighting approaches – MAP prior approach

### Implementation in the NCC package:

```
MAPprior_bin(data = trial_data, arm = 3, alpha = 0.025,  
             prior_prec_tau = 4, prior_prec_eta = 0.001,  
             robustify = TRUE, weight = 0.1)
```

#### Input:

- Data frame with trial data
- Arm to perform inference on
- Decision boundary
- Parameters for prior distributions
- Weight for the non-informative prior component in the robustified MAP

treatment	period	response
0	1	0
1	1	1
0	1	1
...	...	...

## Downweighting approaches – MAP prior approach

Implementation in the NCC package:

```
MAPprior_bin(data = trial_data, arm = 3, alpha = 0.025,  
             prior_prec_tau = 4, prior_prec_eta = 0.001,  
             robustify = TRUE, weight = 0.1)
```

### Input:

- Data frame with trial data
- Arm to perform inference on
- Decision boundary
- Parameters for prior distributions
- Weight for the non-informative prior component in the robustified MAP

treatment	period	response
0	1	0
1	1	1
0	1	1
...	...	...

### Output:

- Posterior probability that the log-odds ratio is less than zero
- Estimated treatment effect in terms of the posterior mean of log-odds ratio
- 95% credible interval for the log-odds ratio
- Indicator of whether the null hypothesis was rejected or not

Analogous function for continuous endpoints:

```
MAPprior_cont(data = trial_data, arm = 3, alpha = 0.025, ...)
```



# How to run a simulation study using the NCC package

- A set of scenarios is analyzed using indicated models
- Inference is performed for given treatment arms
- Probability to reject  $H_0$ , bias and mean squared error of the treatment effect are simulated based on a given number of replications

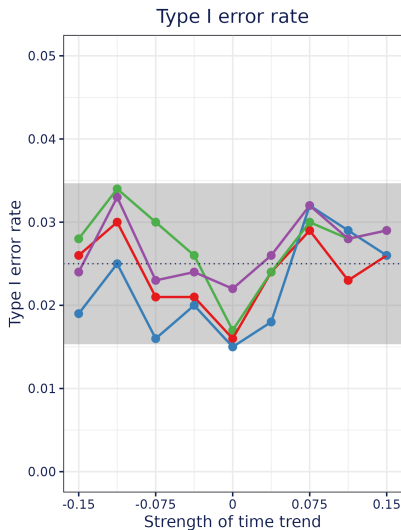
`sim_scenarios:`

num_arms	n_arm	d1	d2	d3	p0	OR1	OR2	OR3	lambda0	lambda1	lambda2	lambda3	trend
3	250	0	250	500	0.5	1	1	1	-0.15	-0.15	-0.15	-0.15	linear
3	250	0	250	500	0.5	1	1	1	0	0	0	0	linear
3	250	0	250	500	0.5	1	1	1	0.15	0.15	0.15	0.15	linear
...	...	...	...	...	...	...	...	...	...	...	...	...	...

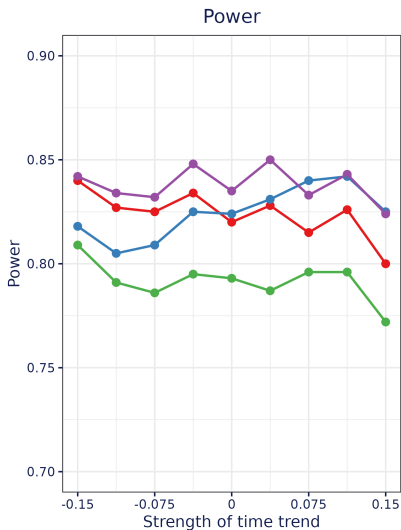
## Performing simulations for a given set of scenarios

```
sim_study_par(nsim = 1000, scenarios = sim_scenarios, arms = 3,  
              models = c("fixmodel", "timemachine", "MAPprior", "sepmode"),  
              endpoint = "bin")
```

# Results of the simulation study



Analysis: ● fixmodel ● MAPprior ● sepmodel ● timemachine



# Conclusions

## The NCC R-package

- Enables **simulation of platform trials** with continuous or binary endpoints under a wide range of scenarios
- Provides the **implementation of analysis methods** for incorporating NCC
- Allows to evaluate the properties and robustness of the implemented methods in **simulation studies**
- Is available on CRAN and comes with an **accompanying website**:  
<https://pavlakrotka.github.io/NCC/>



# Conclusions

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## Ongoing work

- **Alternative models** for incorporating non-concurrent controls
  - Mixed effect models, spline regression
- Further improvements in the package **documentation and website**



## Selected references

- Krotka, P., Hees, K., et al. “*NCC: An R-package for analysis and simulation of platform trials with non-concurrent controls.*” arXiv:2302.12634 (2023).
- Bofill Roig, M., Krotka, P., et al. “*On model-based time trend adjustments in platform trials with non-concurrent controls.*” BMC Medical Research Methodology (2022).
- Saville, B. R., Berry, D. A., et al. “*The Bayesian Time Machine: Accounting for Temporal Drift in Multi-arm Platform Trials.*” Clinical Trials (2022).
- Schmidli, H., Gsteiger, S., et al. “*Robust meta-analytic-predictive priors in clinical trials with historical control information.*” Biometrics (2014).
- Weber, S., Li, Y., et al. “*Applying Meta-Analytic-Predictive Priors with the R Bayesian Evidence Synthesis Tools.*” Journal of Statistical Software (2021).

# Thank you for your attention!



**EU-PEARL**

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