



universität
wien

MASTERARBEIT / MASTER'S THESIS

Titel der Masterarbeit / Title of the Master's Thesis

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

verfasst von / submitted by

Pavla Krotká, BSc

angestrebter akademischer Grad / in partial fulfilment of the requirements for the degree of

Master of Science (MSc)

Wien, 2023 / Vienna, 2023

Studienkennzahl lt. Studienblatt /
degree programme code as it appears on
the student record sheet:

UA 066 645

Studienrichtung lt. Studienblatt /
degree programme as it appears on
the student record sheet:

Masterstudium Data Science

Betreut von / Supervisor:

Univ.-Prof. Dr.rer.nat. Martin Posch

Mitbetreut von / Co-Supervisor:

Dr. Marta Bofill Roig

Acknowledgements

④ I would mention explicitly the contrasts in each ch.

Abstract

in the trial-arm analysis

split outcome

Platform trials enhance drug development by offering increased flexibility and efficiency as compared to traditional randomized clinical trials. They evaluate the efficacy of multiple treatment arms, with the added benefit of permitting treatment arms to enter and leave the trial over time, as new experimental treatments become available. Treatment efficacy is usually assessed using a shared control arm. For arms entering the ongoing trial later, the control data is divided into concurrent and non-concurrent controls, referring to control patients recruited while the given treatment arm is in the platform and before it enters, respectively. Analysis using non-concurrent controls can reduce the required sample size and increase the statistical power, but might also lead to bias in the treatment effect estimates and hypotheses tests, if time trends are present in the trial.

⑤ Aiming at utilizing non-concurrent controls while leading to valid statistical inference, several analysis approaches have been proposed. In particular, a frequentist regression model has been suggested that incorporates non-concurrent data and adjust for potential bias by including the factor "period" as a fixed effect, defining periods as time intervals bounded by any treatment arm entering or leaving the platform. It was shown that this model leads to unbiased treatment effect estimates and asymptotically controls the type I error rate regardless of the time trend pattern, if the time trend affects all arms in the trial equally and is additive on the model scale. ✓

⑥ In this thesis, we suggest two extensions to this modelling strategy. First, we propose an alternative definition of the time covariate by dividing the trial into fixed-length calendar time intervals. Second, we consider more flexible models to adjust for time trends. In particular, we propose including time as a random effect in mixed models. This allows us to additionally account for dependency between closer time intervals by considering autocorrelated random effects. Moreover, we employ spline regression to model time with a smooth polynomial function. *finally, we propose a mix...*

We implement the proposals in the NCC R-package and evaluate their performance in terms of the type I error rate and statistical power for individual treatment-control comparisons in a simulation study under a wide range of scenarios.

⑦ for trials without interim analysis...

→ we create an R package that implements... simulation... wrappers and visualization.

... model fitted with concurrent and non-concurrent data to enhance precision of estimates, while adjusting...

Kurzfassung

Das ist eine deutsche Kurzfassung meiner in Englisch verfassten Masterarbeit.

Contents

Acknowledgements	i
Abstract	iii
Kurzfassung	v
List of Tables	ix
List of Figures	xi
1. Introduction	1
1.1. Randomized Controlled Trials	1
1.2. Platform Trials	2
1.3. Concurrent and Non-concurrent Controls	3
1.4. Software for Designing Complex Clinical Trials	5
1.5. Thesis Contribution	5
2. Methods	7
2.1. Current Methods for Incorporating Non-concurrent Controls	7
2.1.1. Frequentist Model-based Approaches	7
2.1.2. Bayesian Time Machine	9
2.1.3. Network Meta-analysis	10
2.1.4. Open Questions	11
2.2. Extensions to the Frequentist Models for Treatment-Control Comparisons	12
2.2.1. Fixed-effects Models	13
2.2.2. Mixed Models	16
2.2.3. Spline Regression	18
3. Simulations and Results	21
3.1. Considered Designs	21
3.2. Results	24
3.2.1. Setting 1: Extension of Regression Model to Trials with Multiple Arms	24
3.2.2. Setting 2: Alternative Definition of the Time Covariate	28
3.2.3. Setting 3: More Flexible Modelling Approaches: Mixed Models . .	30
3.2.4. Setting 4: More Flexible Modelling Approaches: Spline Regression	31

Contents

4. Software	35
4.1. Software Description	35
4.1.1. Data Simulation	38
4.1.2. Analysis Approaches	39
4.1.3. Trial Data Visualization and Wrapper Functions	41
4.2. Examples	42
4.2.1. How to Analyze Platform Trial Data Utilising Non-concurrent Controls	42
4.2.2. How to Run a Simulation Study	45
5. Conclusion and Discussion	49
5.1. Summary	49
5.2. Future Research	50
Bibliography	53
A. Appendix	57

List of Tables

2.1.	Summary of the used notation.	13
2.2.	Summary of the proposed models.	14
3.1.	Simulation designs and parameters considered in the simulation study. . .	24
4.1.	Main functions of the NCC package with a short description.	37
4.2.	Main input arguments together with a short description and functions included in this article using these arguments. Detailed explanations can be found at https://pavlakrotka.github.io/NCC/	38

List of Figures

1.1.	Testing multiple experimental treatments in different clinical trial frameworks. A) Separate randomized clinical trials, each with its own control group. B) A multi-arm trial, where all interventions enter the trial at the same time. C) A platform trial, permitting the arms to enter and leave at different time points.	3
1.2.	Non-concurrent control data for arm 2.	4
2.1.	Scheme of the platform trial considered in [16] and [17].	8
2.2.	Scheme of the considered general platform trial.	12
2.3.	Illustration of the data set \mathcal{D}_2 . Data taken into account for the evaluation of the 2nd treatment arm are highlighted.	15
3.1.	Mean responses under the null hypothesis under time trends of different patterns and strength of $\lambda = 0.15$	23
3.2.	Illustration of the scenario with 10 experimental arms. In this case, arm i enters after $d_i = 400 \cdot (i - 1)$ patients have been recruited to the trial. We focus on evaluating the efficacy of the 5th experimental treatment arm, highlighted in the figure, compared to the shared control group.	25
3.3.	Type I error rate and power of the fixed effect regression model with period adjustment compared to the pooled and separate analyses with respect to the strength of the time trend λ . In this example, $d = 400$ and linear shape of the time trend are used and the 5th experimental arm is being evaluated.	26
3.4.	Type I error rate and power of the fixed effect regression model with period adjustment compared to the pooled and separate analyses with respect to the timing of adding the treatment arms. In this example, a linear time trend with strength $\lambda = 0.5$ is considered and the 5th experimental arm is being evaluated.	27
3.5.	Type I error rate and power of the regression model with period adjustment compared to the pooled and separate analyses with respect to the index of the evaluated arm. In this example, $d = 200$ and a linear time trend with strength $\lambda = 0.5$ are considered.	27
3.6.	Illustration of the scenario with 4 experimental arms, where arm i enters after $d_i = 250 \cdot (i - 1)$ patients have been recruited to the trial. We focus on evaluating the efficacy of the 3rd experimental treatment arm, highlighted in the figure, compared to the shared control group.	28

List of Figures

3.7.	Type I error rate and power of the regression model with calendar time adjustment compared to the regression model with period adjustment and separate analysis with respect to the size of the calendar time unit under different time trend patterns. In this example, $\lambda = 0.15$ is considered and the 3rd experimental arm is being evaluated.	29
3.8.	Type I error rate and power of the regression model with calendar time adjustment compared to the regression model with period adjustment and separate analysis with respect to the strength of the time trend λ under different time trend patterns. In this example, calendar time unit length of 25 is used and the 3rd experimental arm is being evaluated.	30
3.9.	Type I error rate and power of the mixed model with period and calendar time adjustments as uncorrelated and autocorrelated random effects, compared to the fixed effect regression model with period adjustment with respect to the pattern and strength of the time trend. In case of the calendar time adjustment, unit size of 25 patients was considered. The 3rd experimental arm is being evaluated.	31
3.10.	Illustration of the scenario with 7 experimental arms, where the experimental treatment arms enter after $d = (0, 250, 250, 500, 500, 750, 750)$ patients have been recruited to the trial. We focus on evaluating the efficacy of the 3rd experimental treatment arm, highlighted in the figure, compared to the shared control group.	32
3.11.	Type I error rate for the cubic spline regression model with knots according to periods or calendar time units compared to the regression model with period adjustment with respect to the strength of the time trend λ using different time trend patterns. In this example, the 3rd experimental arm is being evaluated.	33
4.1.	Scheme of the NCC package functions by functionality. Auxiliary functions for data generation are omitted in this figure.	36
4.2.	Time trend patterns with varying parameters.	40
4.3.	Output of the function <code>plot_trial()</code>	43
4.4.	Results of the toy simulation study. Type I error rate, bias and MSE of the treatment effect estimates for treatment arm 4 with respect to the strength of the time trend.	47

1. Introduction

1.1. Randomized Controlled Trials

In the last decades, clinical trials have become the gold standard approach for evaluating the efficacy of new experimental treatments in drug development. In the classical one-to-one design, for a given disease and population, one drug is investigated. Patients receiving this drug are compared to patients in the control arm, which can be either the current standard of care or placebo.

The course of a clinical trial is usually divided into four phases. The aim of phase I is to determine the possible toxic effects and establish the tolerated dose that will be used for further examination. Once the safety and tolerability of the new drug has been assessed in phase I, the drug progresses to phase II, where the therapeutic effects are analyzed. Here, the objective is to prove that the new intervention provides sufficient efficacy to justify further investigation. If this holds, the new drug is compared to the current standard of care for the given disease in a phase III study. This comparative study aims to assess the efficacy and toxicity of the compared treatments in a setting with larger sample sizes. Results from phase III study pose the basis for regulatory agencies to decide whether the new treatment will be approved for the general population. Phase IV study is conducted after the drug has been approved for the market in order to monitor and document rare side effects and other problems that might occur in the population after a longer period of time. ✓

In order to guarantee comparability of the two treatment groups in a phase III study, patients are allocated to the groups randomly. This *randomization* ensures that the assigned treatment is independent of the baseline characteristics. These classical *randomized controlled clinical trials* (RCTs) have been considered the most reliable form of scientific evidence for evaluating drug efficacy, since the randomization reduces spurious causality and bias, which could occur if the physicians or patients were involved in the decision, or could arise from other factors that affect the outcome. If proper randomization is employed, the groups are alike on average, which enables the researchers to make causal inference about the new treatment.

In the traditional setting, the differences in outcomes between these two groups are only assessed in the final analysis at the end of the trial in order to determine whether the new treatment is effective or not. It might, however, be more ethical and economical to monitor the trial data periodically and implement the possibility to stop the trial earlier. The trial should not be carried on, if, for example, one treatment is clearly superior, so that new patients can benefit from this therapy more quickly. In contrast, if the new drug does not offer any benefit, or even poses safety concerns, the trial should be stopped

1. Introduction

early for futility to prevent the administration of this treatment to more patients [1]. Clinical trials that allow for early stopping after an interim analysis are referred to as *group sequential trials*. An interim analysis may be performed at multiple time points.

In group sequential trials, the design parameters, such as the decision rules used in the interim analysis, have to be specified in advance during the planning of the clinical trial. Because of this *pre-specified adaptivity* of group sequential designs, data from the interim analysis cannot be used **to modify the course of the trial**, which reduces the flexibility of the trial design [2]. In the last decades, *adaptive designs* have been introduced that allow design changes to be made during the course of the trial based on interim results. Examples are sample size reassessment, subgroup selection, or endpoint selection. Methods have been proposed to enable these adaptations while controlling the type I error rate and resulting in unbiased estimators. Furthermore, designs have been also proposed that enable investigating multiple drugs and allow the conduct of a phase II and phase III study within one trial, in a *seamless* manner [1].

1.2. Platform Trials

In recent years, the rapid progress in biotechnology has led to the need for even more flexibility in clinical trial designs which has been addressed, among other things, by introducing the so-called *platform trials* [3]. Platform trials are adaptive multi-arm multi-stage clinical trials that aim at evaluating the efficacy of multiple treatments for a single disease simultaneously [4]. The number of experimental treatment arms is not known in advance and the treatments are also allowed to enter and leave the progressing trial. This design enables faster evaluation of drugs that are being developed during the ongoing trial, as they can be directly included to the shared platform. Moreover, platform trials often include interim analyses before the final analysis and modifications of the trial design can be made based on the observed information.

Testing multiple treatments in the classical trial framework requires setting up separate RCTs for all investigated interventions, each one with its own control group, as illustrated in Figure 1.1-A. In platform trials, the control group generally is shared across all treatment arms. Figure 1.1-C illustrates a platform trial with 4 experimental treatment arms and a shared control arm. Due to this sharing of resources, less patients are required to be randomized into the control arm as compared to separate RCTs. This poses an advantage primarily from the ethical and patient perspective. Another unique characteristics of platform trials is that the control may also change in the course of the trial. For instance, if an effective treatment arm becomes the new standard of care.

Due to their higher flexibility, platform trials bring many operational and statistical challenges. In particular, **their planning is much more complex as compared to the classical RCTs and requires extensive computer simulations, since the progress of the trial (i.e. how many experimental arms will be evaluated and the times of their adding and dropping) is not known upfront.** Concerns about multiplicity arise from the fact that multiple experimental treatments are investigated within the trial, which may additionally be tested with regard to multiple endpoints or in multiple subgroups [5]. **An optimal decision**

1.3. Concurrent and Non-concurrent Controls

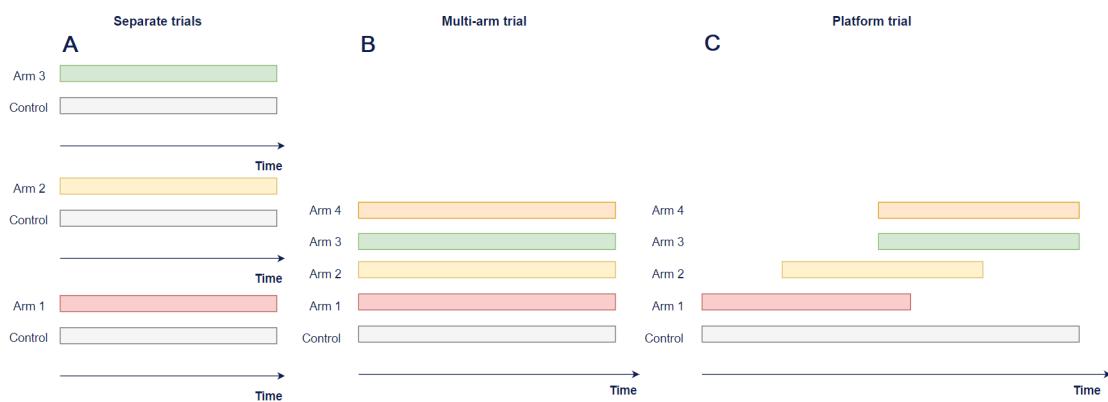


Figure 1.1.: Testing multiple experimental treatments in different clinical trial frameworks.

- A)** Separate randomized clinical trials, each with its own control group.
- B)** A multi-arm trial, where all interventions enter the trial at the same time.
- C)** A platform trial, permitting the arms to enter and leave at different time points.

(i.e., ...)

on the adaptation rules, such as the timing of the interim analyses, stopping rules, and randomization is not trivial, as their choice should not inflate the type I error rate. Challenging is also the definition of estimands (the targets of estimation) as platform trials might have multiple objectives and different estimands might be needed for different treatments. Moreover, estimands may need to be modified in the course of the trial, for example, if the control arm changes [6]. Another statistical issue that has recently been controversially discussed is the use of the shared control group in the trial analysis [7].

I would mention first that all adaptations in platform trials come with challenges for defining the estimands and then at particular care:

- 1) adding new arms
- 2) multiple populations
- 3) control ch.

not sure if this would read better here

1.3. Concurrent and Non-concurrent Controls

In platform trials, for treatment arms that enter when the trial is ongoing, the control group is divided into two separate groups: the *concurrent controls* (CC), which includes patients that were randomized to the control arm at the same time as the given treatment arm was active in the trial; and the *non-concurrent controls* (NCC), which denotes patients randomized to the control group before the evaluated treatment arm entered the platform. Figure 1.2 exemplifies a platform trial with two experimental arms, where the second arm joined the trial later. NCC data for the second arm are highlighted.

The question is if and how to incorporate the NCC data to the analysis of the given treatment arm and there is still no consensus regarding this issue. Including NCC data to the analysis may, on one hand, improve the statistical power of the treatment-control comparison, as the underlying sample size increases. However, bias might be introduced to the analysis, if time trends are present in the trial. Such time trends might be caused for instance by changes in the standard of care, patient population or by seasonal effects. Therefore, appropriate methodology that takes into account possible temporal changes is ✓

1. Introduction

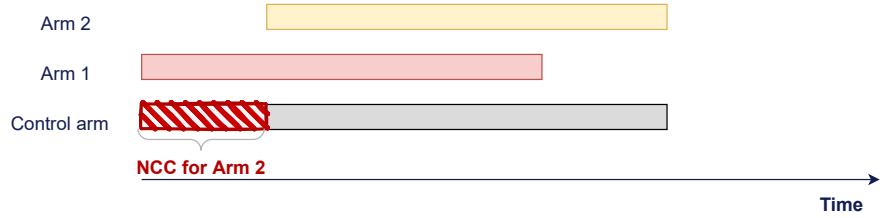


Figure 1.2.: Non-concurrent control data for arm 2.

required in order to analyze such trials properly.

Non-concurrent controls share some characteristics with *historical controls*, as they both refer to data collected prior to the data on the treatment under study, and thus both might introduce calendar time bias if used in the analysis [8]. The underlying difference between historical and non-concurrent controls is that non-concurrent controls comprise patients that have been part of the same randomized trial as the investigated treatment. Hence, both CC and NCC are part of the common trial framework and thus have the same inclusion and exclusion criteria and assessment of the endpoint.

Methods for incorporating historical controls have been widely discussed in the last years, and could be analogously used in the context of platform trials to incorporate NCC data [9].

There are two naive approaches for utilizing historical or non-concurrent controls: the separate and pooled analysis. In the separate approach, the experimental treatment is only compared to the concurrent controls and therefore the historical information is completely discarded. Pooled analysis naively pools CC and NCC data without any adjustments.

Frequentist methods discussed in the context of historical controls include for instance the "test-then-pool" approach, where the distribution of historical and CC data is first tested for equality with a frequentist test and subsequently either separate or pooled analysis is performed based on the rejection or acceptance of the null hypothesis [10]. Another method where historical data is borrowed is the so-called dynamic pooling, where a weight parameter is assigned to the historical data, which controls the proportion of the historical information that will be used in the analysis [11]. Moreover, propensity score methods can be used to balance the differences between historical and concurrent controls [12]. The analysis can also be directly adjusted for the baseline covariates using a frequentist regression model.

As far as Bayesian approaches are concerned, power prior, commensurate power prior and meta-analytic-predictive (MAP) prior approaches for incorporating historical data have been proposed in the literature. Power prior methods down-weight the historical information by introducing a power parameter, whereby the likelihood of the historical data is then raised to this parameter in order to control the amount of borrowing [13]. An extension to the power prior approach is the commensurate prior approach that directly parameterizes the commensurability of the historical and concurrent data and uses this measure to select the power parameter. Hence, the amount of historical data to be used

1.4. Software for Designing Complex Clinical Trials

in the analysis is determined by the comparability of the historical and concurrent data [14]. In the meta-analytic-predictive (MAP) prior approaches, the historical information is used to derive a meta-analytic-predictive prior distribution, which is then combined with the CC data to estimate the response of the control arm [15].

In the specific context of platform trials, model-based approaches have been discussed, which consider linear regression including time as covariate to avoid bias due to time trends [16, 17].



Preq. and Bayesian



1.4. Software for Designing Complex Clinical Trials

In complex designs and especially in platform trials, the use of software to design the trials and to investigate their operating characteristics via simulations has become paramount [3]. Examples of commercial statistical software for that purpose are FACTS [18] and EAST [19].

FACTS (the "Fixed and Adaptive Clinical Trial Simulator"), is a software package developed by Berry Consultants to facilitate the design and statistical analysis of clinical trials. EAST is also a commercial software, particularly devoted to the design, simulation, and monitoring of adaptive, group-sequential and fixed sample size trials. Several open-source R packages are also available. OCTOPUS [20] is an R package which has been developed with the objective of supporting in simulating platform trial designs. MAMS [21] implements the design of multi-arm multi-stage trials with normal, binary, ordinal or time-to-event endpoints within the group-sequential framework. gsDesign [22] and rpact [23] design groups sequential and confirmatory adaptive trial designs and help to describe their properties. SIMPLE [24] (SIMulating PLatform trials Efficiently) is a modular software developed for simulating a wide variety of platform trial designs.

However, to the best of our knowledge, there is no open-source software available implementing the different methodologies that have recently been proposed for the analysis incorporating non-concurrent controls. Moreover, there is a need to provide statistical tools that allow for assessing the properties of the methods when utilising non-concurrent controls and risks of bias in the treatment effect estimates under a wide range of situations, including flexible entry times of experimental treatment arms and time trends of various patterns and strengths.

my?

1.5. Thesis Contribution

This thesis focuses on using non-concurrent controls for individual treatment-control comparisons in platform trials with continuous endpoints in the presence of time trends. In Chapter 2, we first review the current model-based approaches presented in the literature so far and discuss their assumptions and limitations. Second, we introduce novel frequentist model-based methods for incorporating NCC data into the analysis. This comprises extending the current frequentist methods to trials with a flexible number of treatment arms, as well as proposing more advanced modelling approaches for adjusting for the time trend, such as mixed models or polynomial splines. In Chapter 3, we evaluate the performance of the proposed methods in a simulation study and assess the conditions

1. Introduction

under which these approaches lead to valid statistical inference. The proposed methods are implemented in an R package, called **NCC**, together with functions to perform simulations under a wide range of settings. In Chapter 4, we present the package and describe how to use it to simulate platform trials with an arbitrary number of experimental treatment arms and a common control group and assess the efficacy of individual treatments while utilizing NCC data. We finish the master thesis by summarizing the work and discussing further research.



2. Methods

In Section 2.1, we review the current methods for incorporating non-concurrent controls into the analysis of platform trials and discuss the differences and similarities, as well as their limitations. These methods include model-based frequentist approaches, the “Time Machine” Bayesian approach and the network meta-analysis approach.

In Section 2.2, we extend the frequentist model approaches for treatment-control comparisons to more complex platform trials than those considered in the literature so far. Furthermore, we explore different variants of the models by considering different definitions of the time variable and propose novel methods that permit further flexibility in the adjustment.

2.1. Current Methods for Incorporating Non-concurrent Controls

Consider a platform trial design with K experimental treatment arms and a shared control group, where the experimental arms enter and leave the trial at different time points. The duration of the trial can then be split into periods, defined as time intervals bounded by any treatment arm either entering or leaving the platform. Alternatively, the time can be divided into equidistant discrete units of calendar time (e.g., weeks or months).

We denote the experimental treatment arms by k ($k = 1, \dots, K$, ordered by entry time) and the control group by $k = 0$. Furthermore, we denote the periods the trial consists of by s ($s = 1, \dots, S$) and the calendar time units by c ($c = 1, \dots, C$). The total number of patients in the trial is given by N . The response for patient j ($j = 1, \dots, N$) is indicated by y_j , the arm they were allocated to by k_j and the period and calendar time corresponding to their entry time by s_j and c_j , respectively. The observed time of recruitment of patient j is given by t_j .

The focus of this thesis is on continuous endpoints, hence the frequentist model-based approaches will only be discussed in this context. As the Bayesian Time Machine, however, has only been proposed for binary endpoints, it will be described for this type of endpoints.

2.1.1. Frequentist Model-based Approaches

Naive pooling of concurrent and non-concurrent controls leads to type I error rate inflation and biased treatment effect estimators, if time trends are present in the trial [16, 17]. Therefore, methodology that accounts for possible time trends is needed in order to perform valid statistical analysis that includes NCC data.

2. Methods

Focusing on a simple platform trial with $K = 2$ experimental treatment arms, Lee and Wason [16] investigated linear regression models that allow to include non-concurrent control data to the analysis. In particular, they assumed a trial, which starts with only one treatment arm and the control group. The second treatment arm is added to the trial later on and both treatment arms finish at the same time. The resulting trial consists of 2 periods, as illustrated in Fig. 2.1.

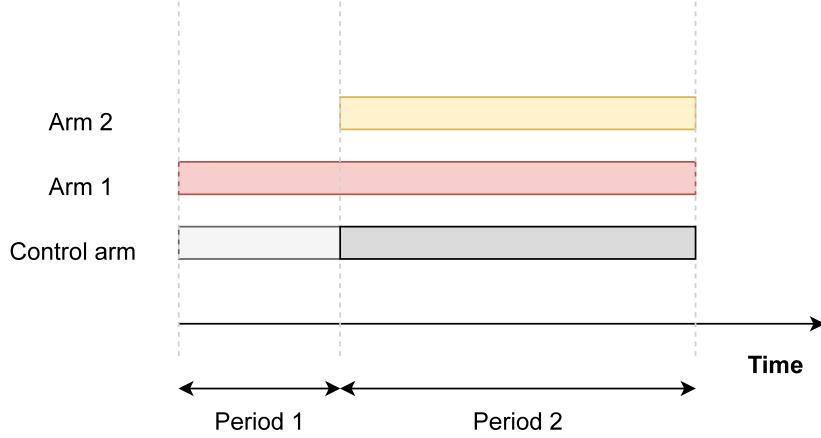


Figure 2.1.: Scheme of the platform trial considered in [16] and [17].

Lee and Wason [16] proposed two linear regression models for evaluating the efficacy of the second treatment arm, which use all data available in the trial (i.e. data from both experimental treatment arms and the control arm). The potential time trends are adjusted for by including the time as a covariate to the model, either in terms of the patient recruitment time (as in (2.1)) or the period indicator (as in (2.2)). The corresponding model equations are as follows:

$$y_j = \eta_0 + \sum_{k=1,2} \theta_k \cdot I(k_j = k) + \gamma \cdot j + \varepsilon_j \quad (2.1)$$

$$y_j = \eta_0 + \sum_{k=1,2} \theta_k \cdot I(k_j = k) + \tau \cdot I(t_j \in s_2) + \varepsilon_j \quad (2.2)$$

where the model intercept η_0 is the response in the control group in the first period and θ_k is the treatment effect for treatment k . The time effect is estimated by the parameters γ and τ . In (2.1), γ represents the effect of continuous recruitment, while in (2.2) τ denotes the time effect between period 1 and 2. The residuals ε_j are assumed to be normally distributed with mean 0 and variance σ^2 ($\varepsilon_j \sim \mathcal{N}(0, \sigma^2)$). Note that both models implicitly assume that the time trend is equal across all arms. However, the first model (2.1) assumes that the time trend is linear with time, while the second one (2.2) models the time trend as constant in every period.

2.1. Current Methods for Incorporating Non-concurrent Controls

Lee and Wason [16] investigated by simulations the operating characteristics of these models when testing the hypothesis $H_{0,2} : \theta_2 = 0$ against the one-sided alternative $H_{1,2} : \theta_2 > 0$, in trials with linear and stepwise time trends that are equal across arms. It was shown that both regression models improve the statistical power as compared to the separate analysis and control the type I error rate, if the functional form of the time trend is correctly specified, the assumption of equal time trends across arms holds and the time effect is additive on the model scale. Moreover, the model with stepwise adjustment (2.2) asymptotically maintains the type I error rate even under misspecification of the functional form of the time trend (e.g., if this is linear instead of stepwise), provided that block randomization is used.

Bofill Roig et al. [17] further investigated these models in trials with time trends that might vary between arms and stated the conditions under which these lead to unbiased treatment effects and type 1 error control. Simulations in [17], showed, also in the context of trials with 2 treatment arms, that the type I error rate control is lost if the time trend in treatment arm 1 differs, and thus when the assumption of equal time trends is violated.

2.1.2. Bayesian Time Machine

A Bayesian method that adjusts for potential time trend in the platform trial, the so-called Bayesian Time Machine, has been introduced by Saville et al. [25]. The Time Machine uses the division of the trial into C calendar time intervals of equal length ("buckets"), which are indexed backwards in time, so that the most recent time interval is denoted by $c = 1$ and the time interval corresponding to the beginning of the trial by $c = C$. The aim is to estimate the treatment effect of the most recently completed treatment arm, while the analysis is performed as soon as the given arm finishes in the trial.

This method has been discussed only in the context of binary endpoints and can be described in terms of a generalized linear model as follows:

$$g(E(y_j)) = \eta_0 + \theta_{k_j} + \alpha_{c_j} \quad (2.3)$$

where y_j is the binary response for patient j and $g(\cdot)$ is the logit link function, which maps the expected value of the patient response to the linear predictors in the model. The model intercept η_0 denotes the response of the control group at time of the analysis, θ_{k_j} is the effect of the treatment arm k that patient j was enrolled in, relative to control. For the parameters η_0 and θ_{k_j} , normal prior distributions are assumed, with mean 0 and variances $\sigma_{\eta_0}^2$ and σ_{θ}^2 , respectively:

$$\begin{aligned} \eta_0 &\sim \mathcal{N}(0, \sigma_{\eta_0}^2) \\ \theta_{k_j} &\sim \mathcal{N}(0, \sigma_{\theta}^2) \end{aligned}$$

In the Time Machine, time trend is represented by α_{c_j} , which is the change in the response in time bucket c_j (which denotes the time bucket in which patient j is enrolled)

2. Methods

compared to the most recent time bucket $c = 1$ and is modelled using a Bayesian second-order normal dynamic linear model. This creates a smoothing over the control response, such that closer time buckets are modelled with more similar response rates:

$$\begin{aligned}\alpha_1 &= 0 \\ \alpha_2 &\sim \mathcal{N}(0, 1/\tau) \\ \alpha_c &\sim \mathcal{N}(2\alpha_{c-1} - \alpha_{c-2}, 1/\tau), \quad 3 \leq c \leq C\end{aligned}$$

where τ denotes the drift parameter that controls the degree of smoothing over the time buckets and is assumed to have a Gamma hyperprior distribution:

$$\tau \sim \text{Gamma}(a, b)$$

Saville et al. [25] examined the operating characteristics of the Time Machine in a simulation study considering a scenario with $K = 5$ treatment arms, focusing only on evaluating the efficacy of the last treatment arm ($k = 5$) against the shared control arm (testing $H_{0,5} : \theta_5 = 1$ vs. $H_{1,5} : \theta_5 > 1$). They show that the Time Machine approximately controls the type I error rate and can lead to superior performance in terms of the statistical power as compared to the frequentist model with categorical adjustment for time in scenarios with linear time trend. However, in situations with sudden changes in the time trend, the frequentist model-based approach is preferable, as the time effect is modelled independently for each time interval in this case.

Similarly to the frequentist model that adjusts for time by including it as a categorical variable, the Bayesian Time Machine relies on the assumption that the time trend affects all arms in the trial equally and is additive on the model scale. Hence there should be no interaction between treatment and time [26]. The Time Machine may also lead to inferior results as compared to the frequentist model in settings with little to no overlap between the treatment arms, as there is not enough data to provide a link between concurrent and non-concurrent controls. Moreover, the performance of the method also depends on the choice of the time buckets, the prior distributions and the values of their corresponding parameters, which need to be chosen individually for a given endpoint, disease and population.

2.1.3. Network Meta-analysis

Marschner and Schou [27] proposed to analyse platform trials using meta-analysis techniques, which allows to conduct both, treatment-control as well as treatment-treatment comparisons for non-concurrent arms. They argued that even though the design of a platform trial is usually adapted over time (e.g. by changing randomization allocations, patient recruitment, by adding and dropping treatment arms, etc.), the periods between these adaptations may still be viewed as separate trials with fixed design. In particular, the randomization and allocation ratio is preserved in each period, hence unbiased direct

2.1. Current Methods for Incorporating Non-concurrent Controls

comparisons can be made between concurrent arms. Moreover, indirect comparisons between two arms across multiple stages can be performed by combining two direct comparisons to a common reference arm, that is concurrent to both arms of interest at some point (i.e. there is an overlap of the reference arm and the arms being compared). From this perspective, the platform trial can be viewed as a network of direct (concurrent) and indirect (non-concurrent) comparisons.

Let $\hat{\boldsymbol{\theta}}$ be a vector containing all direct contrast estimates from all periods, i.e., period-wise estimates of treatment-control comparisons, and also of treatment-treatment comparisons of concurrent treatments. The proposed method linearly combines the estimators from $\hat{\boldsymbol{\theta}}$ to obtain the network estimates $\hat{\boldsymbol{\theta}}^{network}$ of the treatment-control comparisons. This effect estimator can then be written as:

$$\hat{\boldsymbol{\theta}}^{network} = (\mathbf{X}^T \mathbf{W} \mathbf{X})^{-1} \mathbf{X}^T \mathbf{W} \hat{\boldsymbol{\theta}} \quad (2.4)$$

where \mathbf{X} is a design matrix specifying the possible treatment contrasts in all periods the trial and \mathbf{W} is a weight matrix, chosen based on the treatment effect standard errors in each period. This weight matrix also quantifies the contribution of the direct evidence to the overall evidence.

As all previously described approaches for incorporating non-concurrent controls, the validity of the network meta-analysis relies on the assumption that the underlying difference between the compared arms remains the same for all direct and indirect comparisons over time. This assumption can be assessed using formal tests of inconsistency, originally developed in the context of meta-analysis.

2.1.4. Open Questions

Novel methods for incorporating NCC data to the analysis of platform trials make use of all data available in the trial to evaluate the efficacy of a particular treatment arm. In other words, data from other experimental treatment arms is borrowed in order to better estimate the effect of time. To guarantee valid statistical inference when including non-concurrent data, the methods discussed in the literature so far rely on the assumption of equal impact of the time trend on all arms in the platform trial on the model scale [26]. Additionally, the Bayesian method only leads to sound results if the values for the parameters of the prior distributions are chosen appropriately. The discussed methods differ in the way the time variable is defined and adjusted for. While the frequentist regression models and the network meta-analysis approach use the concept of periods defined by adaptations in the trial, the Bayesian approach uses time buckets of equal length, similar to actual calendar times.

In the following section, we propose various extensions to the frequentist regression models with regard to the adjustment for time. In particular, we discuss using calendar time adjustment as an alternative to the period adjustment and consider more flexible adjustment techniques, such as random effects and polynomial splines. In Chapter 3, we evaluate the operating characteristics of the newly proposed methods in a simulation study and state under which conditions they lead to valid statistical inference.

2. Methods

2.2. Extensions to the Frequentist Models for Treatment-Control Comparisons

We extend the frequentist models from [16] and [17] to platform trials with K experimental treatment arms ($K > 2$), indexed by entry order, and a shared control group (for illustration see Fig. 2.2). Moreover, we propose models that adjust for time trend by using periods, as in [16] and [17], as well as using calendar time intervals as in [25], and explore further approaches to model the time trend.

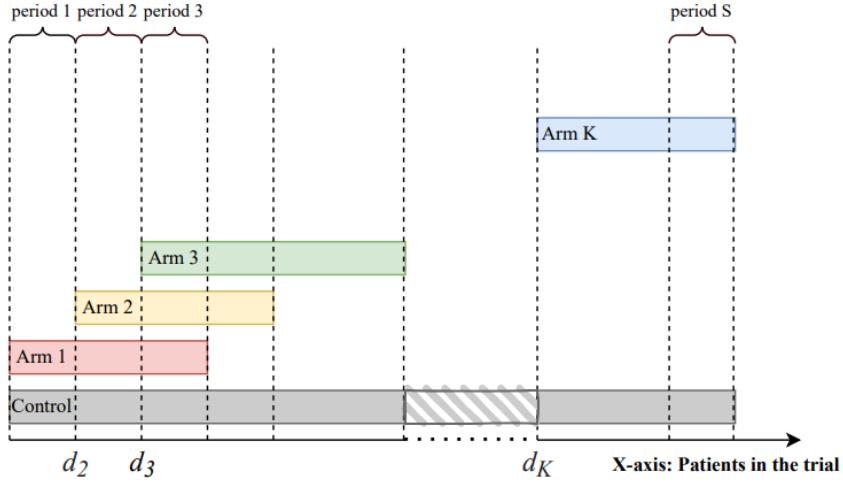


Figure 2.2.: Scheme of the considered general platform trial.

First, we divide the trial into periods, defined as time intervals bounded by adding or dropping experimental treatment arms. Formally, let \mathbf{T}_S be the set of all periods in the trial, $\mathbf{T}_S = \{T_{S_1}, T_{S_2}, \dots, T_{S_S}\}$, where the s -th period is defined by

$$T_{S_s} = (\min\{\max_{\mathbb{P}(k_j=l')>0}\{t_j\}, \min_{\mathbb{P}(k_j=l)>0}\{t_j\}\}, \min\{\max_{\mathbb{P}(k_j=l')>0}\{t_j\}, \min_{\mathbb{P}(k_j=l+1)>0}\{t_j\}\}) \text{ for } s \in \{1, \dots, S\} \text{ and } l, l' \in \{1, \dots, K\}, l \neq l'. \text{ Here } \mathbb{P}(k_j = l) \text{ denotes the probability that patient } j \text{ will be allocated to treatment } l.$$

Dividing the trial into equidistant discrete units of calendar time \mathbf{T} (e.g. months, where $\mathbf{T} = 1$ would correspond to the first month of the trial) is given by the set of intervals $\mathbf{T}_C = \{T_{C_1}, T_{C_2}, \dots, T_{C_C}\}$, where $T_{C_i} = (i-1, i)$, for $i \in \{1, \dots, C\}$.

PENDING: Revise this notation!*

We summarize the notation in Table 2.1

We focus on evaluating treatment arms that enter when the trial is already ongoing and therefore NCC data is available for these arms. We aim at comparing the efficacy of each treatment against the control as soon as the treatment arm is completed. Consider the one-sided null hypothesis $H_{0,M} : \theta_M \leq 0$ for arm M under study, where θ_M denotes the treatment effect size for treatment M . To test the null hypothesis H_{0M} , we propose model-based approaches adjusting for time as fixed or random factor, where time stratified either

2.2. Extensions to the Frequentist Models for Treatment-Control Comparisons

Notation	Definition
K	number of experimental treatment arms
$k = 0, \dots, K$	arm indicator
N	total number of patients in the trial
$j = 1, \dots, N$	patient index
S	total number of periods
$s = 1, \dots, S$	period indicator
C	total number of calendar time units
$c = 1, \dots, C$	calendar time unit indicator
y_j	response of patient j
t_j	patient recruitment time of patient j
θ_k	treatment effect of treatment k
λ_k	strength of the time trend in treatment arm k
d	timing of adding treatment arms
M	currently evaluated treatment arm
S_M	period, in which arm M left the trial
C_M	calendar time unit, in which arm M left the trial
\mathcal{K}_M	set of treatment arms active in the trial prior or up to S_M or C_M

Table 2.1.: Summary of the used notation.

period or by calendar time. Our proposed models use all data from the trial until treatment M leaves the platform (i.e., all data in the set $\mathcal{D}_M = \{(y_j, k_j, t_j), j = 1, \dots, N; t_j \leq \mathbf{T}_M\}$, where \mathbf{T}_M denotes the time in which arm M finishes). Note that also data from unfinished arms is included to the models. The considered models and corresponding time definitions and adjustments for time trend are summarized in Table 2.2.

2.2.1. Fixed-effects Models

Firstly, we consider two linear regression models that estimate the effect of treatments, which were active in the trial prior or up to the time unit \mathbf{T}_M and adjust for potential time trends by including time as a categorical covariate. The two approaches differ in the way time intervals are defined in the model, one using periods and the other the calendar time.

Period Adjustment

In the first model, we adjust for the time effect by including the factor period to the model, i.e., using a step-function:

$$y_j = \eta_0 + \sum_{k \in \mathcal{K}_M} \theta_k \cdot I(k_j = k) + \sum_{s=2}^{S_M} \tau_s \cdot I(t_j \in T_{S_s}) + \varepsilon_j \quad (2.5)$$

2. Methods

Name	Time definition	Time adjustment	Section and reference
Fixed-effect model with period adjustment	period	fixed effect	Section 2.2.1 Equation (2.5)
Fixed-effect model with calendar time adjustment	calendar time	fixed effect	Section 2.2.1 Equation (2.6)
Mixed-effect model with period adjustment and uncorrelated random effects	period	random effect	Section 2.2.2 Equation (2.7)
Mixed-effect model with calendar time adjustment and uncorrelated random effects	calendar time	random effect	Section 2.2.2 Equation (2.8)
Mixed-effect model with period adjustment and autocorrelated random effects	period	random effect	Section 2.2.2 Equation (2.9)
Mixed-effect model with calendar time adjustment and autocorrelated random effects	calendar time	random effect	Section 2.2.2 Equation (2.10)
Spline regression model with knots according to periods	period	polynomial spline	Section 2.2.3 Equation (2.12)
Spline regression model with knots according to calendar times	calendar time	polynomial spline	Section 2.2.3 Equation (2.12)

Table 2.2.: Summary of the proposed models.

where η_0 is the response in the control arm in the first period; θ_k represents the effect of treatment k compared to control for $k \in \mathcal{K}_M$, where \mathcal{K}_M is the set of treatments that were active in the trial during periods prior or up to \mathbf{T}_M ; τ_s indicates the stepwise period effect between periods 1 and s ($s = 2, \dots, S_M$), where S_M denotes the period, in which arm M left the trial (i.e. the period in which \mathbf{T}_M is included).

This approach is a direct extension of the model (2.2), investigated in [16] and [17], to platform trials with more than two treatment arms and periods. A difference here is that data from treatment arms that entered the trial later than the investigated arm M and are not finished yet is also used in the analysis. Since we assume that the time effect is equal across arms and constant over the period, as in [16] and [17], the model relies on the same assumption, that is, additivity on model scale and equal strength of the time trend across arms.

2.2. Extensions to the Frequentist Models for Treatment-Control Comparisons

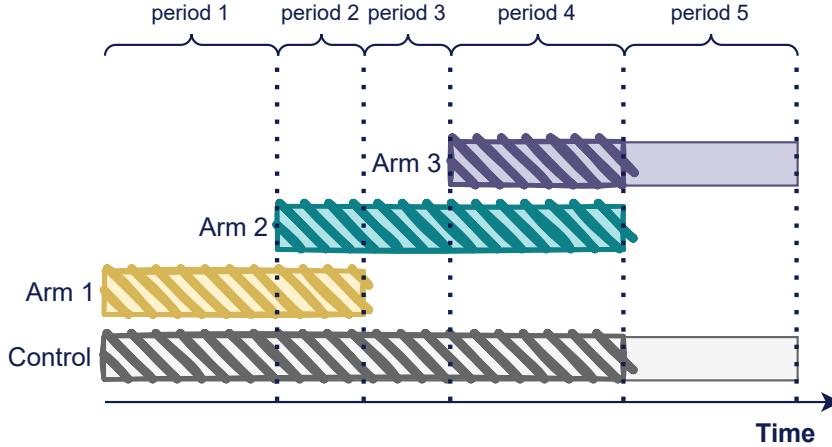


Figure 2.3.: Illustration of the data set \mathcal{D}_2 . Data taken into account for the evaluation of the 2nd treatment arm are highlighted.

Calendar Time Adjustment

In the second approach, we consider a regression model adjusting for the time effect by using calendar time intervals, and thus estimating the calendar time effect rather than period effect:

$$y_j = \eta_0 + \sum_{k \in \mathcal{K}_M} \theta_k \cdot I(k_j = k) + \sum_{c=2}^{C_M} \tau_c \cdot I(t_j \in T_{C_c}) + \varepsilon_j \quad (2.6)$$

Here η_0 represents the control response in the first calendar time unit; θ_k denotes the treatment effect of treatment k compared to control for $k \in \mathcal{K}_M$, and \mathcal{K}_M is the set of treatments that were active up until the arm M left the trial. τ_c is the effect between calendar time units 1 and c ($c = 2, \dots, C_M$), where C_M indicates the calendar time unit, in which arm M left the trial.

The division of the trial into calendar times is depicted in Fig. 2.3. The length of these units is given in terms of the number of enrolled patients and can be specified arbitrarily.

****PENDING: Adapt Fig. 2.3 to also illustrate division into calendar times!****

Note that this model, similarly to the Bayesian Time Machine, divides time into bins of equal length. These bins are, unlike the period adjustment considered in [16] and [17], and in the extended model (2.5), independent of alternations to the trial design, i.e. adding and dropping arms is not taken into account.

As the adjustment in this case is done for each calendar time unit, it is assumed that the time effect is constant in each unit and equal across all arms. Moreover, the length of the time intervals poses an additional design parameter that allows to adjust also for shorter time intervals than are given by the periods.

2. Methods

2.2.2. Mixed Models

In models (2.5) and (2.6), time is treated as a fixed factor. Alternatively, patients within different periods or calendar time units could be considered as different clusters, having a period- or calendar time-specific random intercepts. In what follows, we include the time variable to the models as a random factor. Under such models, the potential correlation between the random effects associated with different periods or calendar times can also be taken into account.

Mixed Models with Uncorrelated Random Effects

First, we consider simple mixed-effect models, where the effects of the given time intervals (period or calendar time units) are assumed to be uncorrelated with the effects of neighbouring intervals. The mixed-effect model with period adjustment has the following form:

$$y_j = \eta_0 + \sum_{k \in \mathcal{K}_M} \theta_k \cdot I(k_j = k) + \sum_{s=2}^{S_M} u_s \cdot I(t_j \in T_{S_s}) + \varepsilon_j \quad (2.7)$$

whereas the model adjusting for calendar time units is given by:

$$y_j = \eta_0 + \sum_{k \in \mathcal{K}_M} \theta_k \cdot I(k_j = k) + \sum_{c=2}^{C_M} u_c \cdot I(t_j \in T_{C_c}) + \varepsilon_j \quad (2.8)$$

where, y_j and θ_k has the same interpretation as in the fixed effect models. The model intercept η_0 is in this case given in terms of the control response across the whole trial up until S_M or C_M , respectively. Note that this interpretation of the intercept is as in the Time Machine approach. u_s and u_c denote the random effect associated with the intercept for period s or calendar time unit c .

The period-specific random effects in (2.7) are assumed to be normally distributed with mean 0 and constant variance σ_{period}^2 :

$$\mathbf{u} \sim \mathcal{N}(0, \sigma_{\text{period}}^2 \cdot I_{S_M \times S_M})$$

The random effects in (2.8) associated with calendar time units are distributed analogously:

$$\mathbf{u} \sim \mathcal{N}(0, \sigma_{\text{calendar}}^2 \cdot I_{C_M \times C_M})$$

Note that in this case the correlation between any two period or calendar time effects is 0.

In both models, the distribution of the residuals ε_j , associated with the response of individual patient j is assumed to be the same for all treatments:

2.2. Extensions to the Frequentist Models for Treatment-Control Comparisons

$$\varepsilon \sim \mathcal{N}(0, \sigma^2 \cdot I_{N \times N})$$

The random effects, u_s or u_c , and the residuals, ε_j , are assumed to be independent.

Mixed Models with Autocorrelated Random Effects

To account for possible correlation of the random effects, we also consider random effects with first-order autoregressive structure (AR(1)), again with period or calendar time adjustments. The model equations are identical to (2.7) and (2.8):

$$y_j = \eta_0 + \sum_{k \in \mathcal{K}_M} \theta_k \cdot I(k_j = k) + \sum_{s=2}^{S_M} u_s \cdot I(t_j \in T_{S_s}) + \varepsilon_j \quad (2.9)$$

$$y_j = \eta_0 + \sum_{k \in \mathcal{K}_M} \theta_k \cdot I(k_j = k) + \sum_{c=2}^{C_M} u_c \cdot I(t_j \in T_{C_c}) + \varepsilon_j \quad (2.10)$$

The model (2.9) considers period adjustments, while (2.10) adjusts for calendar times and the model parameters have the same interpretation as above.

There is a difference, however, with respect to the distribution of the random effects, which are now modelled as autocorrelated. The random effects for individual periods are assumed to be normally distributed with mean 0, constant variance σ_{period}^2 and an AR(1) correlation structure:

$$\mathbf{u} \sim \mathcal{N}(0, \sigma_{period}^2 \cdot \Sigma_{S_M \times S_M})$$

$$\Sigma_{S_M \times S_M} = \begin{bmatrix} 1 & \phi & \dots & \phi^{S_M-1} \\ \phi & 1 & \dots & \phi^{S_M-2} \\ \vdots & \vdots & \ddots & \vdots \\ \phi^{S_M-1} & \phi^{S_M-2} & \dots & 1 \end{bmatrix}$$

Analogous distribution is assumed for the random effects associated with different calendar times:

$$\mathbf{u} \sim \mathcal{N}(0, \sigma_{calendar}^2 \cdot \Sigma_{C_M \times C_M})$$

$$\Sigma_{C_M \times C_M} = \begin{bmatrix} 1 & \phi & \dots & \phi^{C_M-1} \\ \phi & 1 & \dots & \phi^{C_M-2} \\ \vdots & \vdots & \ddots & \vdots \\ \phi^{C_M-1} & \phi^{C_M-2} & \dots & 1 \end{bmatrix}$$

2. Methods

The parameter ϕ denotes the correlation between two adjacent periods or calendar time units. Note that ϕ can range from -1 to 1 and the correlation of periods that are w units apart is equal to ϕ^w , such that the correlation is weaker for periods that are further apart.

The residuals are again assumed to be normally distributed (i.i.d.) with mean 0 and constant variance:

$$\varepsilon \sim \mathcal{N}(0, \sigma^2 \cdot I_{N \times N}) \quad (2.11)$$

2.2.3. Spline Regression

The models in Sections 2.2.1 and 2.2.2 assumed an underlying linear relationship between the patient response and the time. In order to also capture potential non-linearity of the time trend, we consider estimating the patient response using spline regression. The model is given by:

$$y_j = \eta_0 + \sum_{k \in \mathcal{K}_M} \theta_k \cdot I(k_j = k) + f(j) + \varepsilon_j \quad (2.12)$$

where y_j , η_0 and θ_k are defined as in (2.5) and the residuals are $\varepsilon_j \sim \mathcal{N}(0, \sigma^2)$. Note that the treatment effect enters the model as a linear predictor. The time trend is modeled via a continuous function $f(j)$ of the patient index j , which also indicates their entry time.

In particular, we consider the B-spline function to model the time trend. This function is composed of multiple polynomial functions of a given degree q , which are joined together at points called *knots*, such that the whole spline is continuous up to $q - 1$ derivative. In our case, the knots are placed within the range of the patient index j . To define a B-spline function, we first define the knot sequence

$$\zeta_1 = \dots = \zeta_q = \zeta_{q+1} < \zeta_{q+2} < \dots < \zeta_{q+Z+1} < \zeta_{q+Z+2} = \zeta_{q+Z+3} = \dots = \zeta_{2q+Z+2}$$

where the Z knots in the set $\{\zeta_{q+2}, \dots, \zeta_{q+Z+1}\}$ are called *inner knots*, while ζ_{q+1} and ζ_{q+Z+2} are referred to as *boundary knots*. The additional knots $\{\zeta_1, \dots, \zeta_q\}$, as well as $\{\zeta_{q+Z+3}, \dots, \zeta_{Z+2q+2}\}$ are set equal to the boundary knots, even though their choice is essentially arbitrary and only needed because of the later recursive definition of the B-spline.

The function $f(j)$ can then be represented by a set of basis functions $B_i^q(j)$ as follows:

$$f(j) = \sum_{i=1}^{q+Z+1} B_i^q(j) \beta_i$$

where β_i are the associated regression coefficients and the functions $B_i^q(j)$ are defined using the Cox-de Boor recursion formula as follows:

2.2. Extensions to the Frequentist Models for Treatment-Control Comparisons

$$B_i^q(j) = \frac{j - \zeta_i}{\zeta_{i+q} - \zeta_i} B_i^{q-1}(j) + \frac{\zeta_{i+q+1} - j}{\zeta_{i+q+1} - \zeta_{i+1}} B_{i+1}^{q-1}(j), \quad i = 1, \dots, q + Z + 1$$

with

$$B_i^0 = \begin{cases} 1 & \zeta_i \leq j < \zeta_{i+1} \\ 0 & \text{otherwise} \end{cases}$$

and

$$B_i^0 \equiv 0 \text{ if } \zeta_i = \zeta_{i+1}$$

For the positions of the inner knots $\{\zeta_{q+2}, \dots, \zeta_{q+Z+1}\}$, we evaluate two strategies, somewhat analogous to the period and calendar time adjustments in Sections 2.2.1 and 2.2.2. Firstly, we place the inner knots to the beginning of each period $s = 2, \dots, S$, such that one polynomial of degree q is always fitted to each period. In this case, the number of inner knots $Z = S - 1$.

Moreover, we consider placing the inner knots equidistantly, according to the length of the calendar time unit, and thus fitting a polynomial of degree q to each calendar time interval, which leads to $Z = C - 1$.

The boundary knots ζ_{q+1} and ζ_{q+K+2} are always set to 1 and N , respectively, hence to the beginning and end of the trial.

Regarding the degree of the fitted polynomial, we explore linear, quadratic and cubic splines, i.e. $q \in (1, 2, 3)$.

Modeling the time using spline functions gives the model additional flexibility as compared to the previously considered approaches, as now also more complex time trend patterns can be modelled more accurately.

3. Simulations and Results

In the following chapter we assess the performance of the proposed methods in a simulation study. For each model, we evaluate the type I error rate and statistical power under a wide range of scenarios. In Section 3.1, we describe the general design of the platform trials considered in the study and the chosen design parameters. In Section 3.2, we present the results from the study, discuss the properties of the examined methods and the influence of certain design parameters on their operating characteristics.

3.1. Considered Designs

We consider a platform trial with K experimental treatment arms that enter the trial sequentially and a control group that is common to all treatment arms. The timing of adding of the treatment arms is given by $d = (d_1, \dots, d_K)$, where d_i indicates how many patients had already been enrolled to the trial by the time treatment i entered the platform. d_1 is always set to 0 to ensure that the platform trial starts with at least one experimental treatment (for illustration see Fig. 2.2).

We distinguish four settings in which we vary the design according to the objectives of the simulation study:

- **Setting 1:** Trial with $K = 10$ experimental arms and linear time trend pattern, where we vary the strength of the time trend, as well as the timings of adding new treatment arms. We focus on comparing the efficacy of arm $M = 5$ to the shared control group, but also discuss how the power of individual treatment-control comparisons depends on the entry order of the treatment arms. In this setting, we aim at evaluating the generalization of the model-based approach with period adjustment to trials with more than two experimental arms.
- **Setting 2:** Trial with $K = 4$ experimental arms, where we evaluate arm $M = 3$, while varying the pattern and strength of the time trend, as well as the size of the calendar time unit. Here, we aim at comparing the definition of time as calendar time intervals to the period definition in fixed effect models.
- **Setting 3:** Trial with $K = 4$ experimental arms, where we evaluate arm $M = 3$, while varying the pattern and strength of the time trend. In this setting, we evaluate the performance of the mixed models
- **Setting 4:** Trial with $K = 7$ experimental arms, where we evaluate arm $M = 3$, while varying the pattern and strength of the time trend. In this setting, we assess the properties of the spline regression.

3. Simulations and Results

To generate the trial data, we assume equal sample sizes in all treatment arms ($n_k = n = 250, \forall k = 1, \dots, K$) and an allocation ratio of $1 : 1 : \dots : 1$ in each period. Patients are assigned to arms following block randomization with block sizes of $2 \cdot (\#\text{active arms} + 1)$ in every period. Patients are indexed by entry order, assuming that at each time unit exactly one patient is recruited and the time of recruitment and observation of the response are equal. The continuous outcome y_j for patient j is then drawn from a normal distribution according to:

$$y_j \sim \mathcal{N}(\mu, \sigma^2)$$

with

$$\mu = \eta_0 + \sum_{k=1}^K \theta_k \cdot I(k_j = k) + f(j)$$

and

$$\sigma^2 = 1$$

where η_0 and θ_k are response in the control arm and the effect of treatment k . Moreover, time trends of various strengths and shapes may be present in the trial. The time trends are denoted by the function $f(j)$ and their magnitude is given by λ . Following time trend patterns are considered:

- linear time trend: $f(j) = \lambda \cdot \frac{j-1}{N-1}$, where N indicates the total sample size in the trial
- stepwise time trend: $f(j) = \lambda \cdot (w_j - 1)$, where w_j indicates how many treatment arms have already entered the trial at the time patient j was enrolled
- inverted-U trend: $f(j) = \lambda \cdot \frac{j-1}{N-1} (I(j \leq N_p) - I(j > N_p))$, where N indicates the total sample size in the trial and N_p is the point at which the trend turns from positive to negative in terms of the sample size
- seasonal trend: $f(j) = \lambda \cdot \sin(\psi \cdot 2\pi \cdot \frac{j-1}{N-1})$, where N indicates the total sample size in the trial and ψ determines how many cycles the time trend should have

Under the linear time trend the mean response linearly increases with slope λ over time, while under the stepwise time trend there is a jump in the mean response of size λ every time a new arm is added to the trial. In the case of inverted-U time trend, the mean response linearly increases (with slope λ) until the sample size has reached N_p , and linearly decreases afterwards. Seasonal trend may consist of multiple cycles, where the response increases at first and decreases afterwards, while the respective peaks of

3.1. Considered Designs

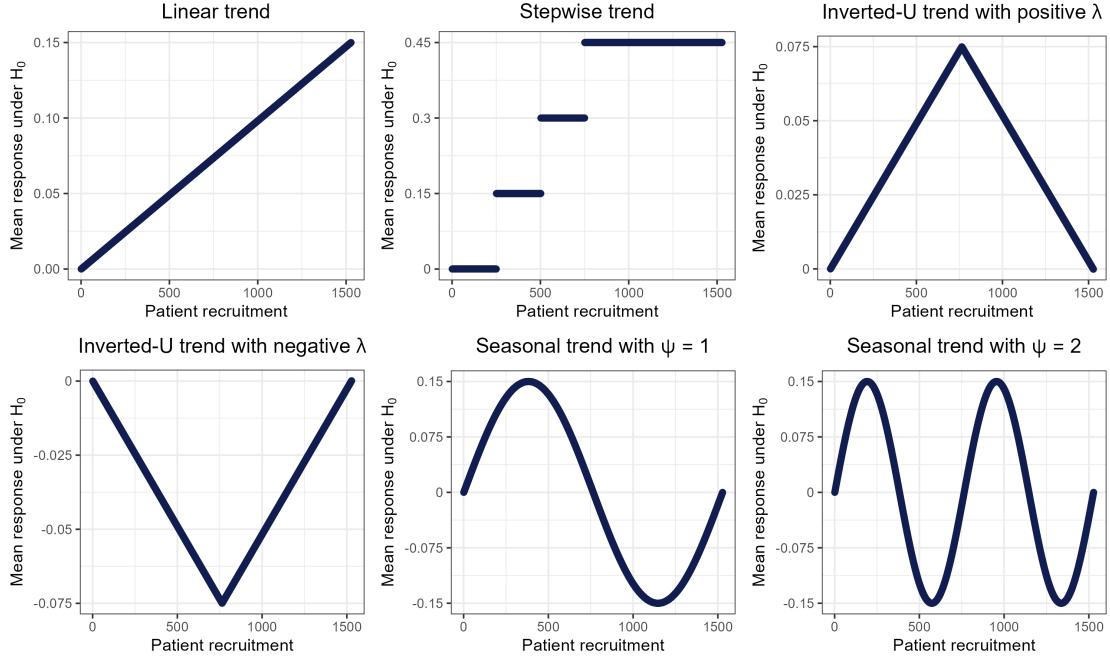


Figure 3.1.: Mean responses under the null hypothesis under time trends of different patterns and strength of $\lambda = 0.15$.

the cycles correspond to λ or $-\lambda$. Mean responses under the null hypothesis under the considered time trend patterns are illustrated in Fig. 3.1.

It is assumed that the equality assumption holds, i.e. the strength of the time trend λ is equal for all arms. Hence, the time trend affects all arms in the same way.

In all cases we use underlying response of zero for the control arm ($\eta_0 = 0$) and a treatment effect of $\theta_k = 0.25$ for treatment arms under the alternative hypothesis. This treatment effect was chosen such that the separate approach achieves approximately 80% power with the given sample size at a one-sided significance level $\alpha = 0.025$.

The strength of the time trend λ , the timings of adding individual treatment arms d , as well as the length of the calendar time units are varied across the scenarios in order to investigate the impact of these parameters on the considered metrics.

Table 3.1 summarizes the considered simulation designs and parameters. We simulated 100,000 replicates of each scenario to estimate the type I error rate and statistical power.

3. Simulations and Results

Setting	K	d	λ	Trend pattern	Calendar time unit size	Objective
Setting 1	10	$d_i = d \cdot (i - 1)$ with $d \in \{0, 100, 200, 300, 400, 500\}$ for $i \in \{1, \dots, 10\}$	$[-0.5, 0.5]$	Linear	-	Evaluate the generalization of the model-based approach with period adjustment
Setting 2	4	$d_i = 250 \cdot (i - 1)$ for $i \in \{1, \dots, 4\}$	$[-0.5, 0.5]$	Linear, stepwise, inverted-U, seasonal	[15, 800]	Evaluate the definition of time as calendar time intervals
Setting 3	4	$d_i = 250 \cdot (i - 1)$ for $i \in \{1, \dots, 4\}$	$[-0.5, 0.5]$	Linear, stepwise, inverted-U, seasonal	25	Evaluate the mixed models
Setting 4	7	$d = (0, 250, 250, 500, 500, 750, 750)$	$[-0.5; 0.5]$	Linear, stepwise, inverted-U, seasonal	25	Evaluate the spline regression

Table 3.1.: Simulation designs and parameters considered in the simulation study.

3.2. Results

We present the results in four sections, corresponding to four different aims of the simulation study, as outlined in Section 3.1. For each aim, we consider a different simulation scenario.

Firstly, in Section 3.2.1, we evaluate the extension the model-based approach with period adjustment, described in Section 2.2.1 in equation (2.5) and assess in particular the impact of overlaps between arms on the operating characteristics of the model.

In Section 3.2.2, we evaluate the calendar time definition of the time covariate in the fixed effect model, given in Section 2.2.1 in equation (2.6). Here, we compare the performance of models with calendar time and period adjustment and discuss the optimal length of the calendar time intervals.

Sections 3.2.3 and 3.2.4 show the performance of the newly proposed flexible modeling approaches for incorporating non-concurrent controls, i.e. linear mixed models from Section 2.2.2 and spline regression described in Section 2.2.3, respectively. The models are evaluated under different patterns and strengths of the time trend.

3.2.1. Setting 1: Extension of Regression Model to Trials with Multiple Arms

Consider a platform trial with 10 experimental treatment arms and a shared control arm, where the experimental arm i enters the trial after $d_i = d \cdot (i - 1)$ patients have been recruited to the platform, as illustrated in Fig. 3.2. Note that d determines the amount of overlapping sample size between the treatment arms. If $d = 0$, all arms join and leave the trial simultaneously, resulting in a standard multi-arm trial and a total overlap between the arms. If $d = 2n$, a new treatment arm enters the trial once the previous one finishes,

3.2. Results

so that there is only one active experimental arm at a time, and hence no overlap between them.

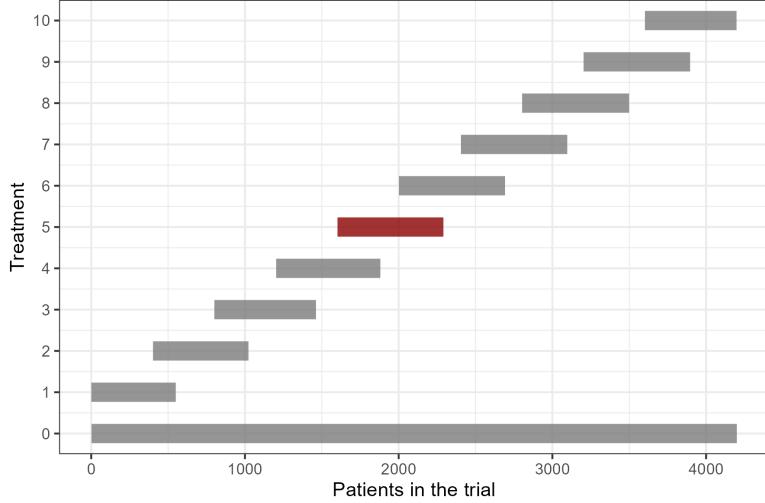


Figure 3.2.: Illustration of the scenario with 10 experimental arms. In this case, arm i enters after $d_i = 400 \cdot (i - 1)$ patients have been recruited to the trial. We focus on evaluating the efficacy of the 5th experimental treatment arm, highlighted in the figure, compared to the shared control group.

We vary the time trend and timing of adding arms as indicated in Table 3.1 in order to evaluate the effect of the overlap and the strength and pattern of the time trend on the type I error rate and statistical power. We compare the linear regression model with period adjustment to the pooled and separate analysis approaches.

Figure 3.3 shows the impact of the strength of the time trend on the operating characteristics when evaluating the 5th experimental arm. The regression model, as well as the separate analysis asymptotically control the type I error rate, regardless of the strength of the time trend. The pooled analysis leads to inflation of the type I error in the presence of positive time trends and deflation in case of negative time trends. Although only results for linear time trends are shown, the regression model maintains the type I error rate under arbitrary time trend pattern. Additionally, the model leads to gain in power as compared to the separate analysis.

The effect of the amount of overlapping sample size is shown in Figure 3.4. The overlaps have no effect on the type I error rate control by the regression model and separate approach, which is guaranteed (asymptotically) in all the cases. The inflation of the pooled analysis gets stronger with increasing d . This is because larger d 's result in longer platform trials and larger size of the NCC data. The power of the regression model, however, depends on the overlap between treatment arms. In the extreme cases with $d = 0$ and $d = 2n$, the regression model leads to identical power as the separate analysis. If $d = 0$, there is no NCC data, as all the arms join the trial at the beginning. Thus, the

3. Simulations and Results

control group used for the treatment-control comparison is the same for both, the separate analysis and the regression model. In case of no overlap between the arms ($d = 2n = 500$), there is insufficient amount of data to estimate the period effect. Hence, simultaneous presence of the experimental arms in the trial is crucial for a reliable estimation of the period effect and resulting power gains when using the regression model.

Figure 3.5 illustrates how the type I error rate and power for individual treatment-control comparisons changes when evaluating different experimental arms in the platform trial. We observe that the power of the regression model increases for arms that were added to the trial later. This is due to larger sample size of the NCC data. On the other hand, this also leads to higher inflation of the pooled analysis.

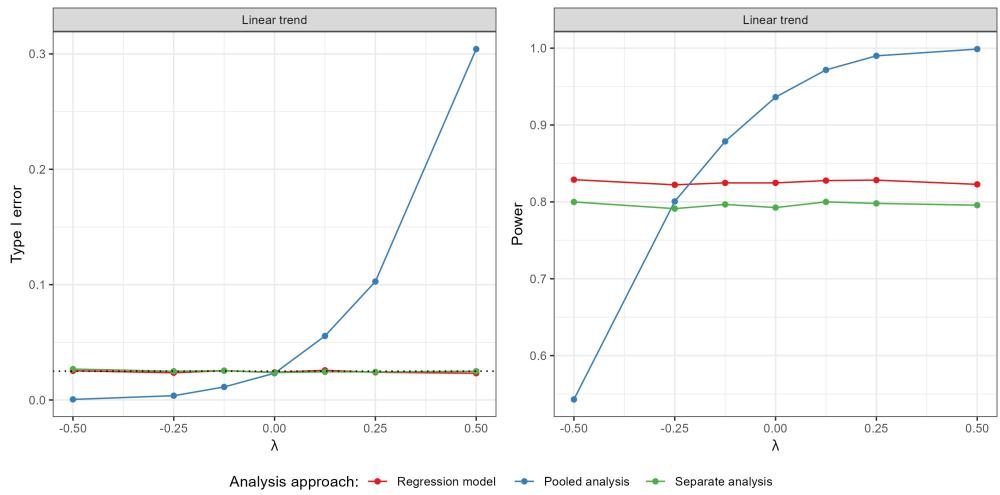


Figure 3.3.: Type I error rate and power of the fixed effect regression model with period adjustment compared to the pooled and separate analyses with respect to the strength of the time trend λ . In this example, $d = 400$ and linear shape of the time trend are used and the 5th experimental arm is being evaluated.

3.2. Results

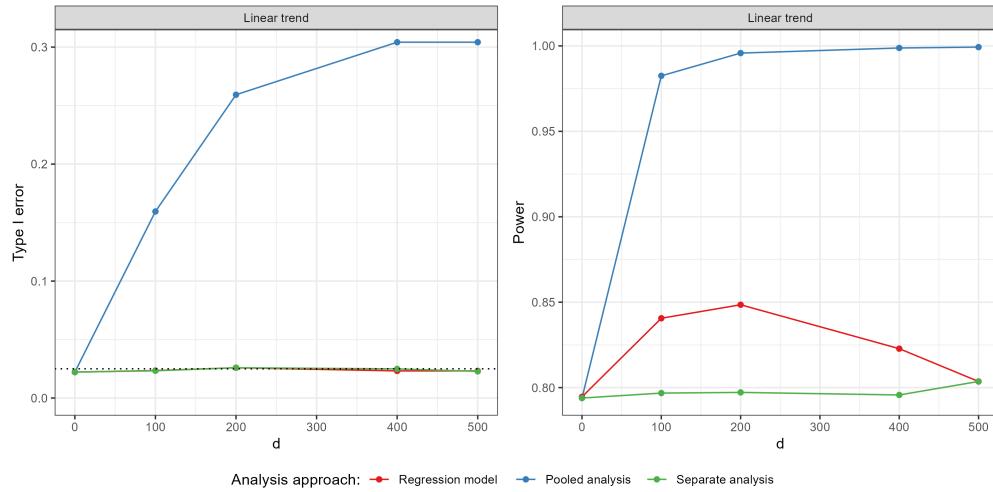


Figure 3.4.: Type I error rate and power of the fixed effect regression model with period adjustment compared to the pooled and separate analyses with respect to the timing of adding the treatment arms. In this example, a linear time trend with strength $\lambda = 0.5$ is considered and the 5th experimental arm is being evaluated.

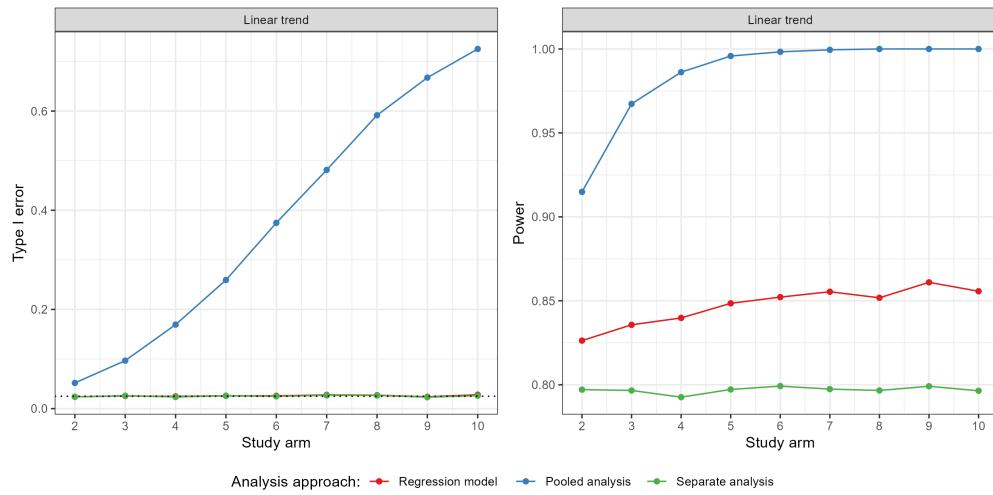


Figure 3.5.: Type I error rate and power of the regression model with period adjustment compared to the pooled and separate analyses with respect to the index of the evaluated arm. In this example, $d = 200$ and a linear time trend with strength $\lambda = 0.5$ are considered.

3. Simulations and Results

3.2.2. Setting 2: Alternative Definition of the Time Covariate

To examine the regression model with calendar time adjustment, we consider a platform trial with 4 experimental treatment arms, where arm i enters after $d_i = 250 \cdot (i - 1)$, leading to a total sample size of 1528 patients. The considered scenario is shown in Figure 3.6. We assess how the model performance depends on the pattern and strength of the time trend, as well as on the chosen calendar time length.

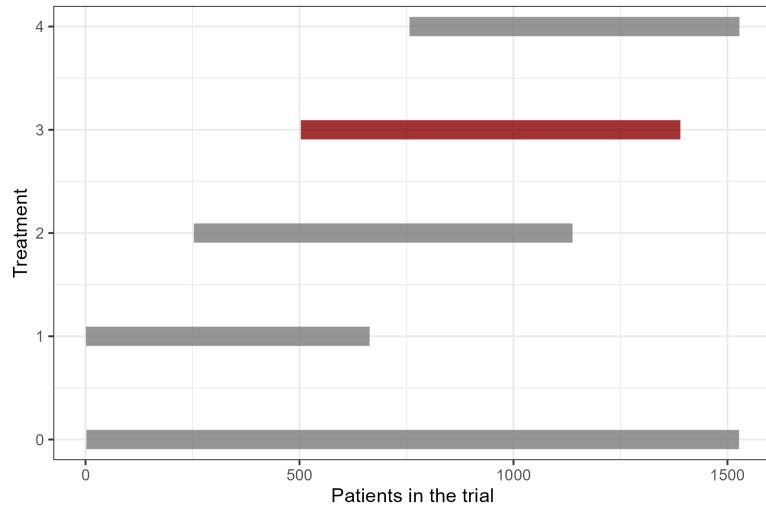


Figure 3.6.: Illustration of the scenario with 4 experimental arms, where arm i enters after $d_i = 250 \cdot (i - 1)$ patients have been recruited to the trial. We focus on evaluating the efficacy of the 3rd experimental treatment arm, highlighted in the figure, compared to the shared control group.

In Figures 3.7 and 3.8 the type I error and power of the model with the calendar time adjustment is compared to the period adjustment and the separate analysis under varying unit size and λ , respectively. The type I error rate control for different time unit lengths is dependent on the time trend pattern. In case of linear and inverted-U trend, the type I error rate is maintained for moderately sized calendar time units, and slightly inflated for units larger than 600 patients. Under the seasonal time trend, we observe deflation of the type I error for unit sizes ≥ 200 . In case of the stepwise trend, the type I error rate control is only given for very small units (< 50 patients). Depending on the unit size, the model with calendar time adjustment can lead to power improvements as compared to the period adjustment, especially in the setting with inverted-U or linear time trend. Nevertheless, as the type I error rate is not maintained in all cases, the choice of the interval length and the resulting trade-off between type I and type II errors needs to be carefully assessed.

3.2. Results

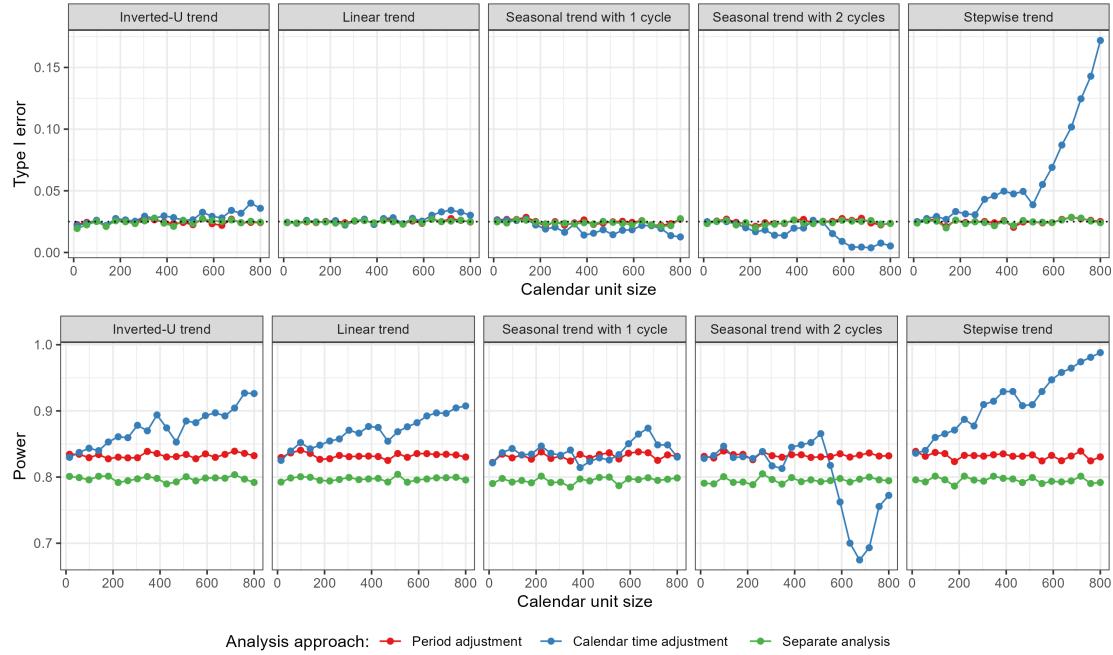


Figure 3.7.: Type I error rate and power of the regression model with calendar time adjustment compared to the regression model with period adjustment and separate analysis with respect to the size of the calendar time unit under different time trend patterns. In this example, $\lambda = 0.15$ is considered and the 3rd experimental arm is being evaluated.

3. Simulations and Results

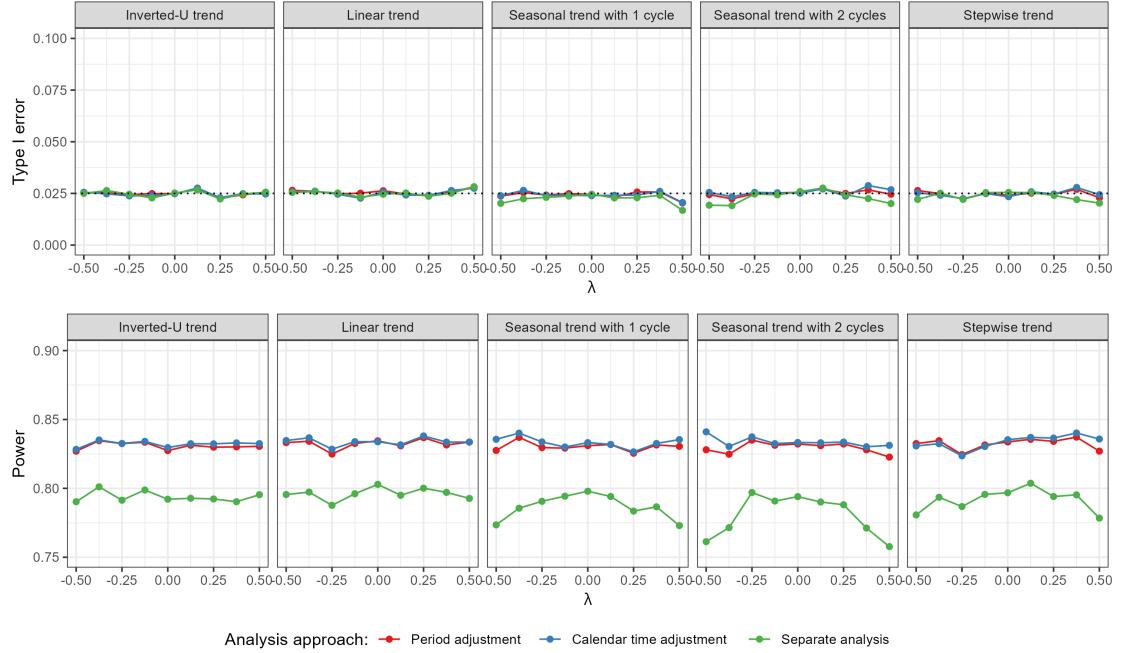


Figure 3.8.: Type I error rate and power of the regression model with calendar time adjustment compared to the regression model with period adjustment and separate analysis with respect to the strength of the time trend λ under different time trend patterns. In this example, calendar time unit length of 25 is used and the 3rd experimental arm is being evaluated.

****PENDING:** Run simulations for Fig. 3.8 with larger unit size to see power improvements of the cal. time adjustment.**

3.2.3. Setting 3: More Flexible Modelling Approaches: Mixed Models

Staying in a setting with four experimental treatment arms (for illustration see Figure 3.6), we analyze the performance of the proposed variants of linear mixed models that include the time covariate as a random effect. We consider varying time trend patterns and strengths and present the resulting type I error rate and power of the mixed models in Figure 3.9, along with the reference model - fixed effect model with period adjustment.

We observe that the mixed models only maintain the type I error rate if no time trends are present in the trial (i.e., $\lambda = 0$). Under this assumption, they also lead to power improvement compared to the fixed effect regression model. However, in case of time trends the type I error rate control is lost. The inflation (or deflation) of the type I error is most pronounced in the mixed model that adjusts for periods as autocorrelated random effects. Moreover, especially in settings with seasonal and stepwise trend, the maximum inflation seems to be achieved for moderately strong time trends. This is because the

3.2. Results

mixed models shrink the effect of the time trend, since it is modelled as a random effect. If, however, the trend is large enough, there is less shrinkage and the time effect is preserved and adjusted for.

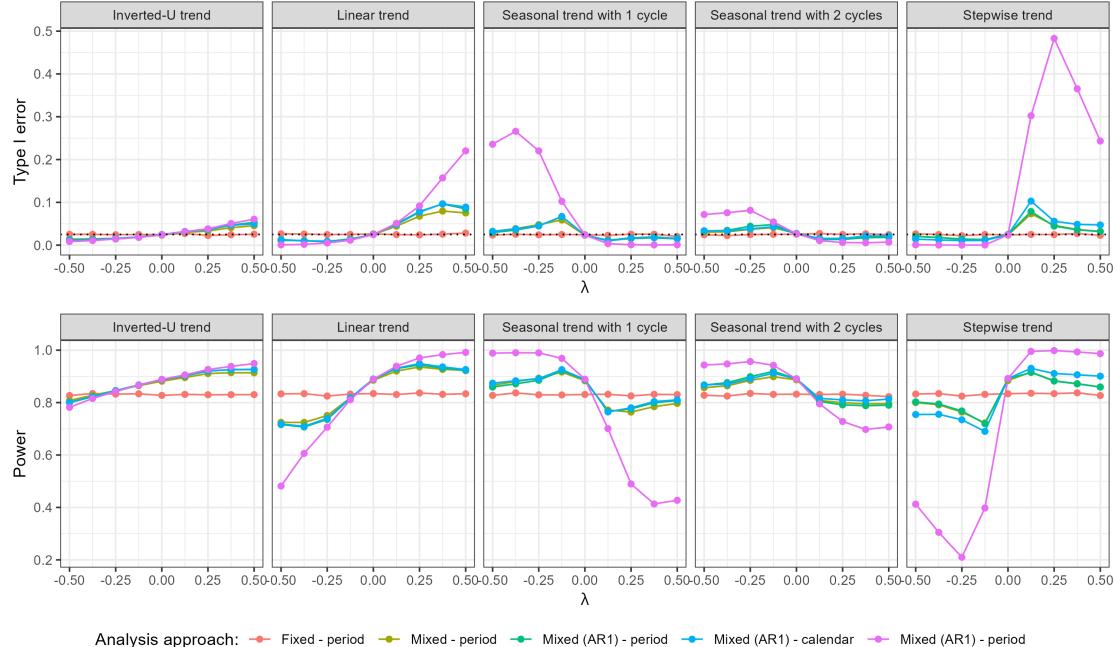


Figure 3.9.: Type I error rate and power of the mixed model with period and calendar time adjustments as uncorrelated and autocorrelated random effects, compared to the fixed effect regression model with period adjustment with respect to the pattern and strength of the time trend. In case of the calendar time adjustment, unit size of 25 patients was considered. The 3rd experimental arm is being evaluated.

3.2.4. Setting 4: More Flexible Modelling Approaches: Spline Regression

The performance of the spline regression models is assessed in a scenario with 7 experimental treatment arms, where some of them enter and leave the trial simultaneously (see Figure 3.10 for illustration). The models are examined under different time trend patterns with varying strength, as described in Table 3.1.

In our simulations, we also varied the degree of the B-splines, considering linear, quadratic and cubic splines. However, since the difference in the resulting operating characteristics were only marginal, we only present results for the cubic spline regression, where the knots are placed either to the beginning of each period or each calendar time interval. Again, we use the fixed effects model with period adjustment as reference.

The type I error rate of the evaluated models under the considered scenarios is presented

3. Simulations and Results

in Figure 3.11. If the time trend pattern is given by a continuous function, the spline regression maintains the type I error rate. However, in case of the stepwise time trend, we observe an inflation in the type I error rate, particularly pronounced when placing the knots according to the periods. This is because the spline regression estimates the time effect by a smooth function, composed of multiple polynomial functions joined together in the knots. This is not an optimal approach if there are sudden jumps in the time trend. In the considered scenarios, the power of the spline regression models was not improved as compared to the fixed effect model.

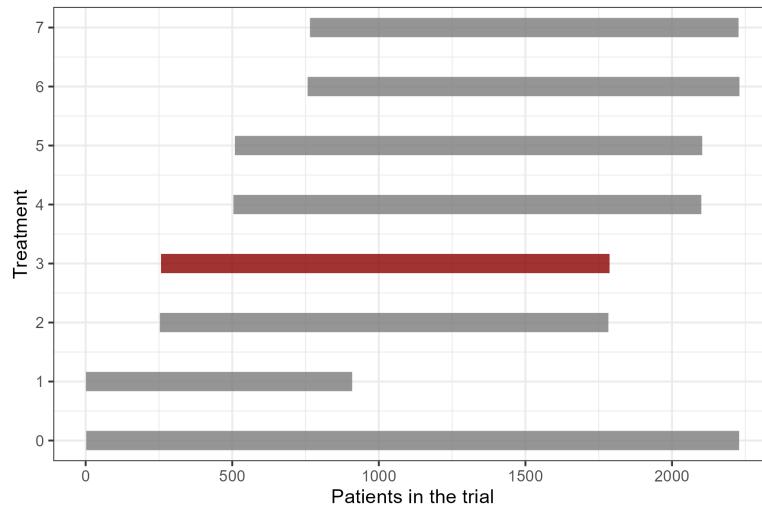


Figure 3.10.: Illustration of the scenario with 7 experimental arms, where the experimental treatment arms enter after $d = (0, 250, 250, 500, 500, 750, 750)$ patients have been recruited to the trial. We focus on evaluating the efficacy of the 3rd experimental treatment arm, highlighted in the figure, compared to the shared control group.

3.2. Results

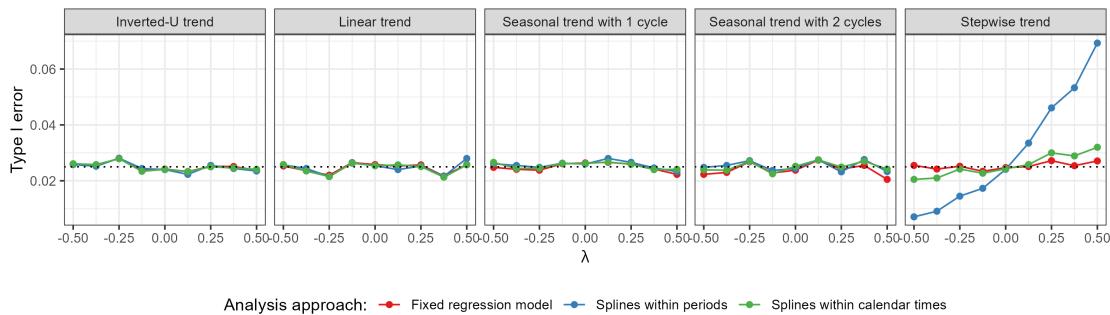


Figure 3.11.: Type I error rate for the cubic spline regression model with knots according to periods or calendar time units compared to the regression model with period adjustment with respect to the strength of the time trend λ using different time trend patterns. In this example, the 3rd experimental arm is being evaluated.

The NCC package has been already mentioned in an article where...

introduced

4. Software

Specially, this package includes not only the proposed models in Section 2.2, but also the freq. models... (see next xx) and the Bayesian Time machine (NCC ver. XX).

In the following chapter, we introduce the R-package NCC, which allows for simulation and analysis of flexible platform trials with non-concurrent controls. All analysis methods proposed in Section 2.2 are implemented in this package, along with two Bayesian approaches for analyzing platform trials with non concurrent controls - the Time Machine approach and the Meta-Analytic-Predictive (MAP) Prior approach. Moreover, the package contains functions for data generation and wrapper functions for running simulation studies. An accompanying paper describing the functionalities of the package "NCC: An R-package for analysis and simulation of platform trials with non-concurrent controls" is currently under review in the Software journal, ~~are described~~.

In Section 4.1 we describe how the package is structured, which functions it contains, and their respective input and output values.

Section 4.2 shows specific examples how to use the NCC R-package to generate and analyze platform trial data and run simulation studies.

4.1. Software Description

and available on arXiv [xx] the article entitled "..."

We present the R-package NCC [29], which was developed for assessing the operating characteristics of analysis methods that utilize non-concurrent controls in the analysis of platform trials. The NCC package provides functions to simulate platform trials with continuous or binary endpoints, as well as functions to analyse the trial data using various approaches, allowing for the incorporation of NCC data. It can be installed either from CRAN (Comprehensive R Archive Network) or Github using the following commands:

```
# devtools::install_github("pavlakrotka/NCC") # Github installation (development version)
> install.packages("NCC") # CRAN installation (stable version)
> library(NCC)
```

The package comes with an accompanying website with background explanations and short tutorials: <https://pavlakrotka.github.io/NCC/>.

The NCC package focuses on trials with continuous or binary endpoints and consists of 34 functions. Some of the functions are implemented for continuous endpoints and some for binary endpoints. The functions with the suffix _cont refer to functions for simulation and analysis of trials with continuous endpoints, while _bin refers to binary endpoints. The NCC functions can be grouped into three main categories according to their functionality: data simulation, analysis, and visualization and wrappers. See Table 4.1 for a summary of the main functions. Figure 4.1 outlines the package structure.

also mention that it is already on CRAN.

4. Software

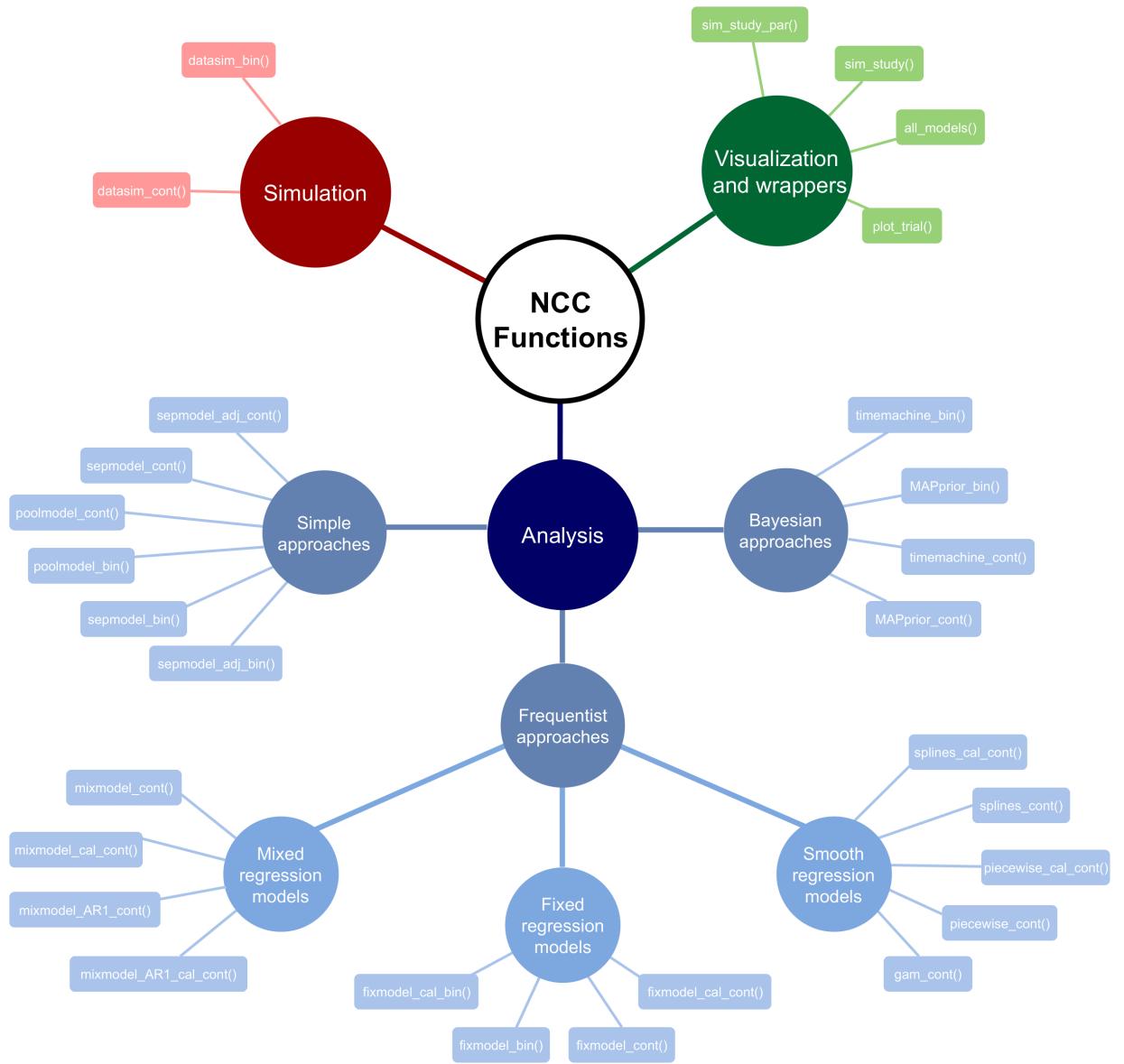


Figure 4.1.: Scheme of the NCC package functions by functionality. Auxiliary functions for data generation are omitted in this figure.

4.1. Software Description

Function	Description	Functionality
<code>datasim_cont()</code>	Simulates trials with continuous endpoints	Data simulation
<code>datasim_bin()</code>	Simulates trials with binary endpoints	Data simulation
<code>get_ss_matrix()</code>	Computes sample sizes per arm and period	Data simulation
<code>linear_trend()</code>	Generates a linear time trend	Data simulation
<code>sw_trend()</code>	Generates a step-wise time trend	Data simulation
<code>inv_u_trend()</code>	Generates a inverted-u time trend	Data simulation
<code>seasonal_trend()</code>	Generates a seasonal time trend	Data simulation
<code>fixmodel_bin()</code>	Performs analysis using a regression model adjusting for periods for binary data	Data analysis
<code>fixmodel_cont()</code>	Performs analysis using a regression model adjusting for periods for continuous data	Data analysis
<code>fixmodel_cal_bin()</code>	Performs analysis using a regression model adjusting for calendar times for binary data	Data analysis
<code>fixmodel_cal_cont()</code>	Performs analysis using a regression model adjusting for calendar times for continuous data	Data analysis
<code>poolmodel_bin()</code>	Performs pooled analysis for binary data	Data analysis
<code>poolmodel_cont()</code>	Performs pooled analysis for continuous data	Data analysis
<code>sepmodel_bin()</code>	Performs separate analysis for binary data	Data analysis
<code>sepmodel_cont()</code>	Performs separate analysis for continuous data	Data analysis
<code>mixmodel_cont()</code>	Performs analysis using a mixed model adjusting for periods as a random factor for continuous data	Data analysis
<code>mixmodel_cal_cont()</code>	Performs analysis using a mixed model adjusting for calendar times as a random factor for continuous data	Data analysis
<code>mixmodel_AR1_cont()</code>	Performs analysis using a mixed model adjusting for periods as a random factor with AR1 correlation structure for continuous data	Data analysis
<code>mixmodel_AR1_cal_cont()</code>	Performs analysis using a mixed model adjusting for calendar times with AR1 correlation structure as a random factor for continuous data	Data analysis
<code>splines_cont()</code>	Performs analysis using regression splines with knots placed according to periods for continuous data	Data analysis
<code>splines_cal_cont()</code>	Performs analysis using regression splines with knots placed according to calendar times for continuous data	Data analysis
<code>plot_trial()</code>	Visualizes the simulated trial over time	Data visualization
<code>sim_study_par()</code>	Performs a simulation study with given scenarios	Wrapper function

Table 4.1.: Main functions of the NCC package with a short description.

The functions `datasim_cont()` and `datasim_bin()` refer to the simulation of patient data from a platform trial; functions such as `fixmodel_cont()`, `mixmodel_cont()` or `splines_cont()` are functions devoted to comparing the efficacy of an experimental treatment versus control using concurrent and non-concurrent controls in trials with continuous endpoints. Finally, the functions `plot_trial()` and `sim_study_par()` are intended to visualise the generated trials and perform simulation studies, respectively.

Most functions in the NCC package use common arguments. The main arguments are briefly described in Table 4.2, together with the functions which rely on them.

Argument	Description	Functions
<code>num_arms</code>	Number of treatment arms in the trial	<code>datasim_bin()</code> , <code>datasim_cont()</code>
<code>n_arm</code>	Sample size per experimental treatment arm	<code>datasim_bin()</code> , <code>datasim_cont()</code>
<code>d</code>	Timings of adding new arms in terms of number of patients recruited to the trial	<code>datasim_bin()</code> , <code>datasim_cont()</code>

4. Software

p0	Response in the control arm for platform trials with binary endpoints	<code>datasim_bin()</code>
mu0	Response in the control arm for platform trials with continuous endpoints	<code>datasim_cont()</code>
OR	Odds ratios for each treatment arm compared to control	<code>datasim_bin()</code>
theta	Treatment effects for each treatment arm	<code>datasim_cont()</code>
sigma	Standard deviation of the responses	<code>datasim_cont()</code>
lambda	Strength of time trend in each arm	<code>datasim_bin(), datasim_cont()</code>
trend	Time trend pattern	<code>datasim_bin(), datasim_cont()</code>
data	Trial data, e.g. generated with the <code>datasim_*</code> () functions	<code>fixmodel_bin(), fixmodel_cont(), fixmodel_cal_bin(), fixmodel_cal_cont(), mixmodel_cont(), mixmodel_cal_cont(), mixmodel_AR1_cont(), mixmodel_AR1_cal_cont(), splines_cont(), splines_cal_cont(), sepmodel_bin(), sepmodel_cont(), poolmodel_bin(), poolmodel_cont()</code>
arm	Treatment arm under study to perform inference on	<code>fixmodel_bin(), fixmodel_cont(), fixmodel_cal_bin(), fixmodel_cal_cont(), mixmodel_cont(), mixmodel_cal_cont(), mixmodel_AR1_cont(), mixmodel_AR1_cal_cont(), splines_cont(), splines_cal_cont(), sepmodel_bin(), sepmodel_cont(), poolmodel_bin(), poolmodel_cont()</code>
alpha	Significance level	<code>fixmodel_bin(), fixmodel_cont(), fixmodel_cal_bin(), fixmodel_cal_cont(), mixmodel_cont(), mixmodel_cal_cont(), mixmodel_AR1_cont(), mixmodel_AR1_cal_cont(), splines_cont(), splines_cal_cont(), sepmodel_bin(), sepmodel_cont(), poolmodel_bin(), poolmodel_cont()</code>
ncc	Whether to include NCC data into the analysis	<code>fixmodel_bin(), fixmodel_cont(), fixmodel_cal_bin(), fixmodel_cal_cont(), mixmodel_cont(), mixmodel_cal_cont(), mixmodel_AR1_cont(), mixmodel_AR1_cal_cont(), splines_cont(), splines_cal_cont(), sepmodel_bin(), sepmodel_cont(), poolmodel_bin(), poolmodel_cont()</code>
unit_size	Number of patients per calendar time unit	<code>fixmodel_cal_bin(), fixmodel_cal_cont(), mixmodel_cal_cont(), mixmodel_AR1_cal_cont(), splines_cal_cont()</code>
bs_degree	Degree of the polynomial spline	<code>splines_cont(), splines_cal_cont()</code>

Table 4.2.: Main input arguments together with a short description and functions included in this article using these arguments. Detailed explanations can be found at <https://pavlakrotka.github.io/NCC/>.

As this thesis deals with platform trials with continuous endpoints, we will focus on describing the functions for this type of endpoints.

4.1.1. Data Simulation

Platform trials with a continuous outcome are simulated using the function `datasim_cont()`, as follows:

refer more to the website and
the appendix (manual)
for further info.

4.1. Software Description

```
> datasim_cont(num_arms, n_arm, d, period_blocks = 2, mu0 = 0,
   theta, lambda, sigma, trend, N_peak, n_wave,
   full = FALSE, check = TRUE)
```

The arguments are the number of experimental treatment arms (`num_arms`), as well as their sample size (`n_arm`), timings of entering the trial in terms of patients already enrolled in the trial to this point (`d`) and treatment effects in terms of the difference in means (`theta`). The control mean is given by the argument `mu0` and has a default value of 0. The standard deviation of the responses is specified by the input argument `sigma` and is assumed to be equal for all arms. Moreover, it is assumed that the sample sizes in each experimental arm are equal. Patients are assigned to the arms according to block randomization using an allocation ratio of 1:1....:1 in each period. For each period, the block size equals to `period_blocks`·(number of arms active in that period) is used. For instance, if `period_blocks=2`, in a period with 2 experimental treatment arms and one control arm, the resulting block size would be 6. The function allows to simulate trial data in the presence of time trends of different patterns and strengths, which can also be specified in the input arguments. The time trend pattern can be specified by means of the argument `trend`, choosing from the options linear, stepwise, inverted-U with a peak at time `N_peak` and seasonal with `n_wave` cycles, while the strength of the trend is indicated by the argument `lambda`. Figure 4.2 shows how the mean response changes under different time trend patterns when varying the parameters `lambda`, `N_peak` and `n_wave`. The argument `full` specifies if the output is given solely in the form of a data frame (if `full=FALSE`) with the trial data, or if the full output is provided in the form of a list, including the trial data and additional information (`full=TRUE`). Finally, `check` is an indicator of whether the input parameters are checked to ensure that they are correctly specified. If `check=TRUE`, the function returns helpful error messages in case of wrong input.

By default, the function returns the simulated trial data in the form of a data frame containing the following columns:

- `j` - patient recruitment index
- `response` - response for patient j
- `treatment` - indicator of the treatment patient j was allocated in
- `period` - indicator of the period in which patient j was recruited in

Simulation of binary endpoints is performed analogously, using the function `datasim_bin()`, which only differs in the indication of the control response (argument `p0`) and the treatment effects (argument `OR`), which are specified in terms of the odds ratio.

4.1.2. Analysis Approaches

The main frequentist analysis approaches for continuous data implemented in the `NCC` package are the fixed and mixed effects, as well as spline regression models with adjustment

4. Software

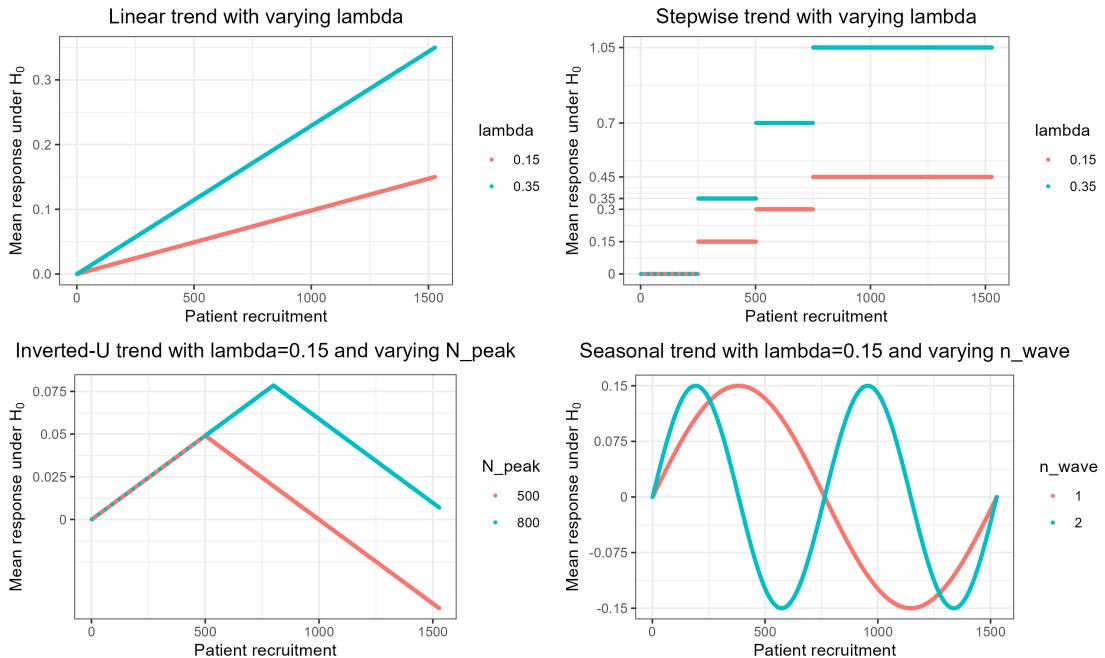


Figure 4.2.: Time trend patterns with varying parameters.

either based on the periods or calendar times. The arguments common to all analysis functions in the **NCC** package are the data frame with the trial data, consisting of columns named "j", "response", "treatment" and "period" (**data**), the indicator of the experimental treatment arm that should be compared to the control group (**arm**) and the significance level (**alpha**).

To analyze the data using the frequentist fixed effects model from equation (2.5), one can use the **fixmodel_cont()** function as follows:

```
> fixmodel_cont(data, arm, alpha = 0.025, ...)
```

The function **mixmodel_cont()** permits to analyse the data using the mixed effects model described by equation (2.7) by means of:

```
> mixmodel_cont(data, arm, alpha = 0.025, ...)
```

To fit the spline regression model from equation (2.12), one can use the function **splines_cont()** with the following syntax:

```
> splines_cont(data, arm, alpha = 0.025, bs_degree = 3, ...)
```

where the parameter **bs_degree** indicates the degree of used the polynomial spline, with a default value of 3 for a cubic spline.

By default, to test H_0 , ... ?

4.1. Software Description

The above presented functions use the definition of time in terms of periods in the trial. Hence, the fixed and mixed models include the factor period and the spline regression places the inner knots at the beginning of each period. Analogous functions for the calendar time adjustment, indicated by the extension _cal (e.g. `fixmodel_cal_cont()`), are also implemented in the package.

The functions perform the respective analysis of the given dataset to compare the efficacy of a specific treatment against control, thus testing the null hypothesis for the treatment effect of the arm under study $H_0 : \theta_{\text{arm}} = 0$ against the one-sided alternative $H_1 : \theta_{\text{arm}} > 0$. To test H_0 , by default all trial data until the evaluated treatment arm leaves the trial are taken into account (i.e., also including data from unfinished arms that joined the platform up to the final analysis of the given treatment arm).

The output of the analysis functions is in the form of a list, containing the one-sided p-value, estimated treatment effect, $(1-\alpha)\cdot100\%$ confidence interval (i.e., 95% CI if `alpha=0.025`), an indicator of whether the null hypothesis was rejected or not, and the fitted model. Functions for spline regression additionally output the position of the inner knots in terms of patient index.

4.1.3. Trial Data Visualization and Wrapper Functions

The package also includes functions to visualise the platform trial data and wrapper functions for performing simulation studies under different scenarios .

The visualization function `plot_trial()` uses as argument a vector with treatment indicators ordered by time (`treatments`) and outputs a plot of the trial progress over time, as we will illustrate in Section 4.2. The main wrapper function is `sim_study_par()`, which permits to efficiently run simulation studies using parallel computing. The code is parallelized on replication level, i.e. replications of one scenario are distributed over the available cores. Using this function requires creating a data frame with the desired simulation scenarios beforehand, which is then used as input to the function (argument `scenarios`) as follows:

```
> sim_study_par(nsims, scenarios, arms,
                 models = c("fixmodel", "sepmodel", "poolmodel"),
                 endpoint, perc_cores = 0.9)
```

where the remaining arguments specify how many times each scenario is to be replicated (`nsim`), the treatment arms that will be evaluated (`arms`), the considered analysis approaches (`models`), the indication of endpoint (`endpoint`) and the (approximate) percentage of available cores that should be used for the simulations (`perc_cores`). The output of `sim_study_par` is a data frame with all considered scenarios and corresponding results, that is, the probability to reject the null hypothesis, the bias, and the mean squared error (MSE) of the treatment effect estimates for each evaluated treatment arm and each considered analysis method.

type of endpoint?

4. Software

4.2. Examples

4.2.1. How to Analyze Platform Trial Data Utilising Non-concurrent Controls

Assume a platform trial with a shared control and three experimental treatment arms entering sequentially, where the second and third treatment arms enter after 100 and 250 patients are recruited to the trial, respectively. Furthermore, assume sample sizes of 100 and treatment effects of 0.25 in each experimental arm, as well as a standard deviation of the responses equal to 1. The mean response for all arms increases by 0.15, whenever a new arm is added to the trial. The data of this hypothetical trial can be simulated using the `datasim_cont()` function:

```
> set.seed(5)
> trial_data <- datasim_cont(num_arms = 3, n_arm = 100, d = c(0, 100, 250),
  theta = rep(0.25, 3), lambda = rep(0.15, 4),
  sigma = 1, trend = "stepwise_2")
```

The generated data is structured as follows:

```
> head(trial_data)
  j      response treatment period
1 1  0.78575816        1       1
2 2 -0.14030110        0       1
3 3 -0.36289414        0       1
4 4 -0.31737256        1       1
5 5  1.41623385        0       1
6 6 -0.04480078        0       1
```

where the patient index is given in the first column, followed by the continuous responses, the treatment arm indicator and finally the period allocation.

In order to illustrate the active treatment arms over time, we use the function `plot_trial()`, whose output is shown in Figure 4.3.

```
> plot_trial(trial_data$treatment)
```

4.2. Examples

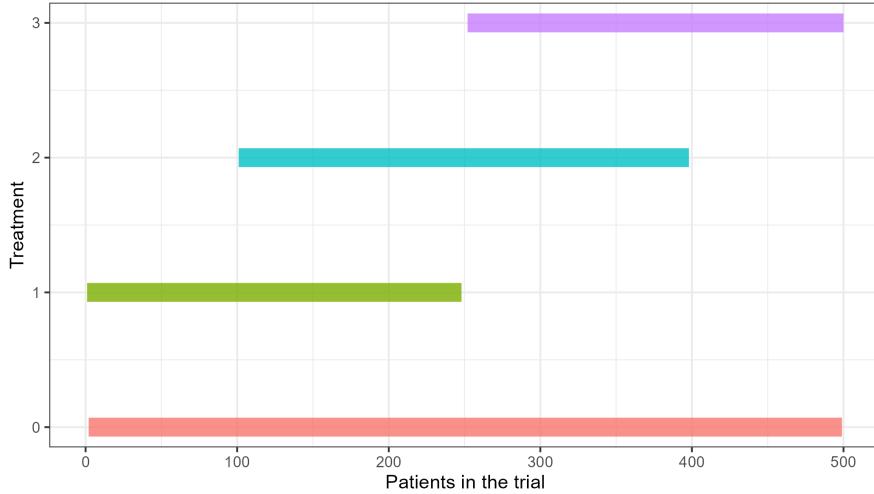


Figure 4.3.: Output of the function `plot_trial()`.

The figure helps to display the entry and exit of arms into and out of the trial over time and to visualize the overlaps between arms more easily.

When the third arm ends, we want to evaluate its efficacy compared to the control using different frequentist model-based approaches. First, we consider a fixed regression model with period adjustment for time trend (as in (2.5)), which is fitted using the `fixmodel_cont()` function:

```
> fixmodel_cont(trial_data, arm = 3, alpha = 0.025)
$p_val
[1] 0.01816827
$treat_effect
[1] 0.2790546
$lower_ci
[1] 0.01782669
$upper_ci
[1] 0.5402824
$reject_h0
[1] TRUE
```

Analysis using a fixed regression model with calendar time adjustment (given by (2.6)) can be performed by means of the `fixmodel_cal_cont()` function. The length of the calendar time interval to adjust for (in terms of the recruited patients) is given by the argument `unit_size`.

```
> fixmodel_cal_cont(trial_data, arm = 3, unit_size = 25, alpha = 0.025)
$p_val
[1] 0.0218659
```

4. Software

```
$treat_effect
[1] 0.2712733
$lower_ci
[1] 0.007656746
$upper_ci
[1] 0.5348899
$reject_h0
[1] TRUE
```

A mixed effect model with period adjustment that assumes uncorrelated random effects (see equation (2.7)) is implemented in the `mixmodel_cont()` function:

```
> mixmodel_cont(trial_data, arm = 3, ci = TRUE, alpha = 0.025)
$p_val
[1] 0.00231647
$treat_effect
[1] 0.3392225
$lower_ci
[1] 0.1059671
$upper_ci
[1] 0.572476
$reject_h0
[1] TRUE
```

Finally, if we want to adjust for time using cubic splines (see equation (2.12)), we can do so by means of the `splines_cont()` function:

```
> splines_cont(trial_data, arm = 3, bs_degree = 3, alpha = 0.025)
$p_val
[1] 0.01686
$treat_effect
[1] 0.2795447
$lower_ci
[1] 0.02160482
$upper_ci
[1] 0.5374847
$reject_h0
[1] TRUE
$knots
[1] 100 250 400
```

In the output of each analysis function, the first element of the list is the p-value (`p_val`) corresponding to testing the null hypothesis $H_0 : \theta_3 = 0$, followed by the estimated treatment effect in terms of difference of the mean response of the evaluated

4.2. Examples

treatment and the control mean (`treat_effect`) and the respective lower and upper confidence limits (`lower_ci`, `upper_ci`). The list also includes a binary indicator of (`p_val < alpha`), i.e., whether the null hypothesis can be rejected on the specified significance level (`reject_h0`). In the considered case, the null hypothesis is rejected by all models, which implies that treatment arm 3 is efficacious. The output of the spline regression also includes the positions of the inner knots, which are in this case placed to the beginning of each period. Furthermore, each output includes the respective fitted regression model (`model`), which is here omitted for simplicity. However, the fitted model can be further analysed using the conventional R functions for generalized linear models, such as `summary(fixmodel_cont(data = trial_data, arm = 3)$model)`. ✓

4.2.2. How to Run a Simulation Study ↪ link to Ch3?

Next, we consider the design of a platform trial with four experimental treatment arms entering sequentially. Aiming to assess the robustness of analysis methods that utilise non-concurrent controls in the presence of time trends, we want to perform a simulation study using the `NCC` package. For this, we first create a data frame with the desired scenarios that contains all the parameters needed for data generation and analysis.

```
> lambda_values <- rep(seq(-0.15, 0.15, length.out = 9), 2)
> sim_scenarios <- data.frame(num_arms = 4,
                                n_arm = 250,
                                d1 = 250*0,
                                d2 = 250*1,
                                d3 = 250*2,
                                d4 = 250*3,
                                period_blocks = 2,
                                mu0 = 0,
                                sigma = 1,
                                theta1 = 0,
                                theta2 = 0,
                                theta3 = 0,
                                theta4 = 0,
                                lambda0 = lambda_values,
                                lambda1 = lambda_values,
                                lambda2 = lambda_values,
                                lambda3 = lambda_values,
                                lambda4 = lambda_values,
                                trend = c(rep("linear", 9), rep("stepwise_2", 9)),
                                alpha = 0.025)
```

We assume here that the null hypothesis holds for all experimental arms (`theta1=...=theta4=0`). We vary the strength (`lambda`) and pattern (`trend`) of the time trend, in order to investigate their impact on the type I error rate, bias and mean squared error (MSE) of the treatment effect estimates. Note, however, that the time trend is equal across arms. ✓

4. Software

We use the function `sim_study_par()` to perform a simulation study with the created scenarios. Here, we evaluate the 4th experimental treatment arm using regression models with period adjustment as fixed or uncorrelated random effect, as well as cubic spline regression and compare their operating characteristics to the separate approach, where only CC data is used for the analysis and the pooled analysis, which naively pools CC and NCC data without further adjustments. Each scenario will be replicated 1000 times.

```
> sim_results <- sim_study_par(nsim = 1000,
                                scenarios = sim_scenarios,
                                arms = 4,
                                models = c("fixmodel",
                                           "mixmodel",
                                           "splines",
                                           "sepmodel",
                                           "poolmodel"),
                                endpoint = "cont",
                                verbose = TRUE)
```

By default (if `verbose=TRUE`), the function reports the system time after each scenario finishes in order to track the progress of the simulations. These messages can be suppressed by setting `verbose=FALSE`.

The resulting data frame contains the considered scenarios and simulation results. The results include the probability of rejecting the null hypothesis, bias and MSE of the treatment effect estimates. We can now visualize the performance of the considered analysis methods with respect to the strength and pattern of the time trend. Figure 4.4 depicts the type I error, bias and MSE with respect to the strength of the time trend and according to the pattern of the time trend. The results show that the pooled analysis and the mixed model lead to inflation of the type I error rate in the presence of positive time trend and its deflation if there are negative time trends. The separate approach and the regression model with period as fixed effect control the type I error rate and yield unbiased treatment effect estimates. As we are using relatively weak time trends in this example, the cubic spline regression control the type I error in case of both, linear and stepwise time trend. However, we can observe slight bias in the treatment effect estimates in the case with stepwise time trend.

link
to Uh3?

4.2. Examples

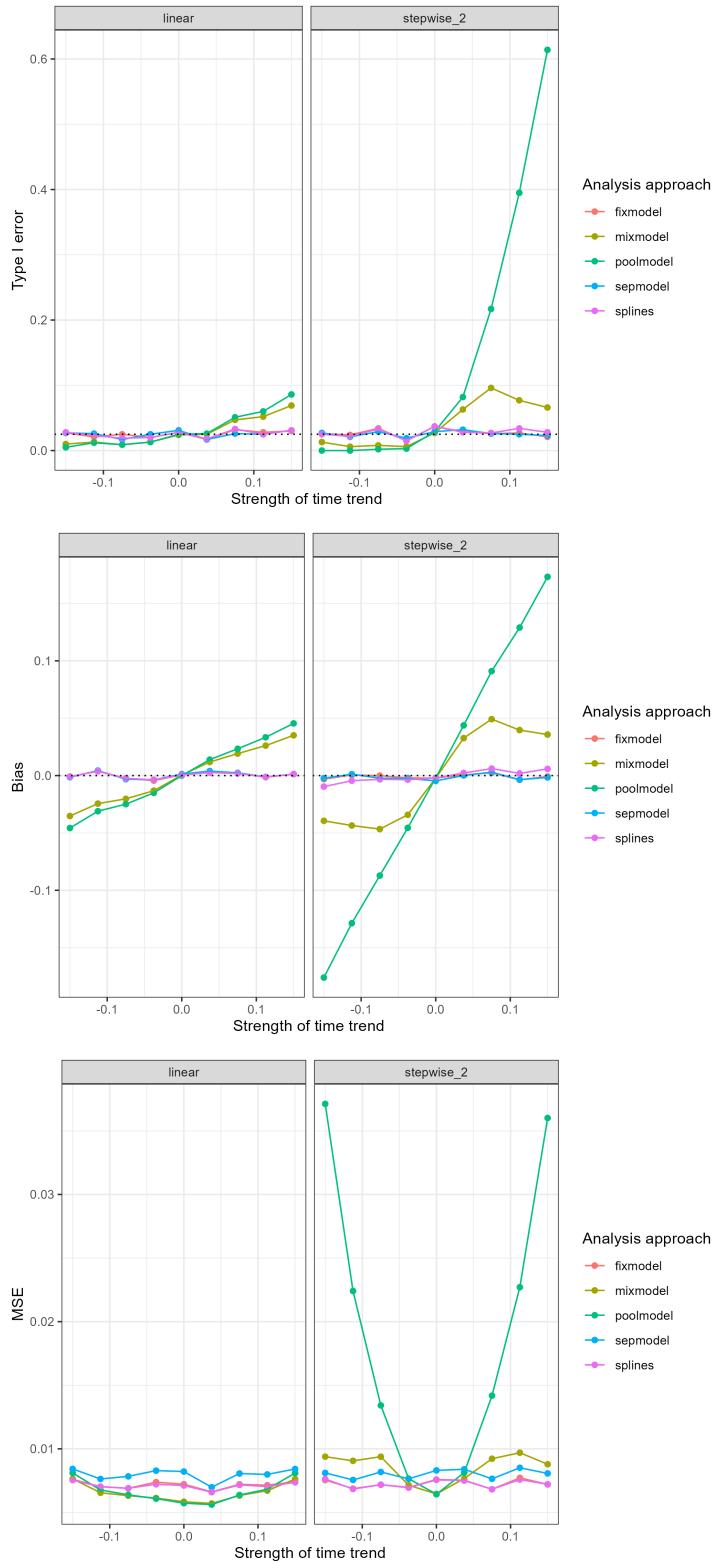


Figure 4.4.: Results of the toy simulation study. Type I error rate, bias and MSE of the treatment effect estimates for treatment arm 4 with respect to the strength of the time trend.

5. Conclusion and Discussion

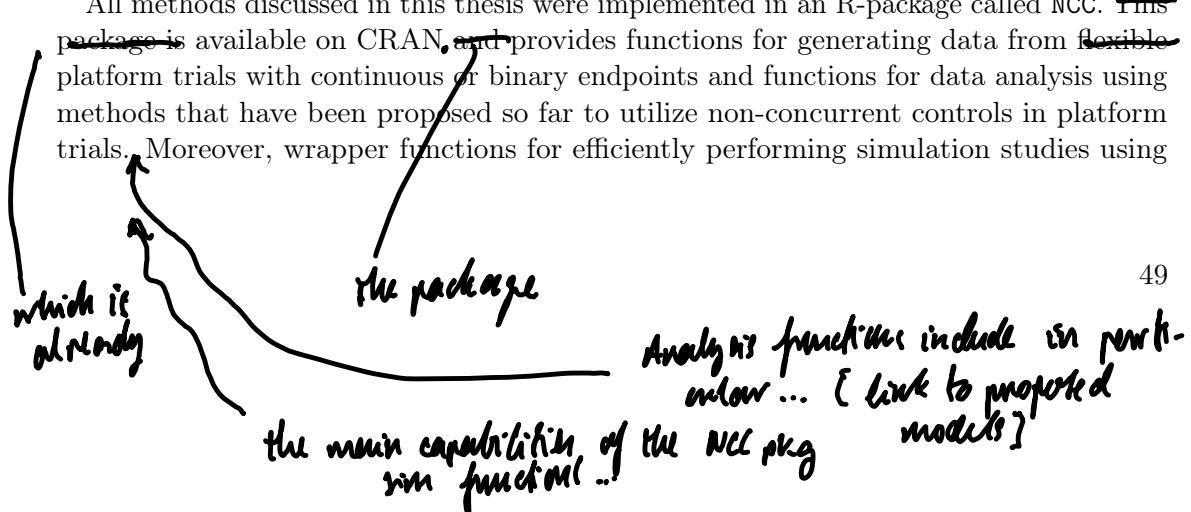
5.1. Summary

The use of non-concurrent controls in the analysis of platform trials has been a subject of lively discussions and intense methodological research during recent years. Frequentist and Bayesian methods that address the issue of possible time trends in the trial and lead to unbiased treatment effect estimates have been proposed and evaluated in complex simulation studies.

In this thesis, we extended the currently available frequentist methods and proposed novel model-based approaches to utilize non-concurrent controls for individual treatment-control comparisons. We generalized the model-based approach with period adjustment, which has been proposed in the context of platform trials with two experimental arms, to more complex trials with a flexible number of treatment arms. Moreover, we introduced an alternative definition of the time covariate, where the duration of the trial is divided in calendar time intervals of equal length. We also considered more flexible means of modelling the time trend. In particular, we proposed adding the time covariate as a random effect in a linear mixed model. In these models, we additionally allowed for autocorrelation between the random effects in order to account for dependency between closer time intervals. Furthermore, we employed B-splines to model time with a polynomial function in a spline regression. Here we consider two options of placing the inner knots - either according to the periods in the trial or according to the calendar time intervals.

We evaluated the performance of the proposed methods in terms of the type I error rate and statistical power in a simulation study, considering a wide range of scenarios. We validated the properties of the fixed effect model adjusting for periods, which had been stated in a setting with two arms, in more complex trials and specified under which conditions this model leads to power gains as compared to the separate analysis. Moreover, we showed the the calendar time adjustment in fixed effect models can in certain scenarios lead to power gains as compared to the period adjustment, while still controlling the type I error. In our scenarios, the mixed models were not suitable for evaluating the efficacy of late entering treatment arms in the presence of time trend. Furthermore, we demonstrated via simulations that modelling time via spline function controls the type I error rate if the shape of the time trend is given by a continuous function.

All methods discussed in this thesis were implemented in an R-package called NCC. ~~This package is available on CRAN and provides functions for generating data from flexible platform trials with continuous or binary endpoints and functions for data analysis using methods that have been proposed so far to utilize non-concurrent controls in platform trials. Moreover, wrapper functions for efficiently performing simulation studies using~~



5. Conclusion and Discussion

parallel computing are available in the package, which facilitate the evaluation of the performance and robustness of the methods in different settings. To our knowledge, this is the only R-package with tools for assessing the properties of methods that incorporate non-concurrent controls to the analysis of platform trials in the presence of time trends. The package can help statisticians in industry or regulators to decide whether the use of non-concurrent controls is appropriate and provide basis for discussing the trial design under different scenarios.



5.2. Future Research

Despite recent advances in statistical methodology for using non-concurrent controls when analyzing platform trials, many questions still remain unanswered. Below we outline some of the open questions that were out of the scope of this thesis, but are potential topics for future research.



Platform Trials with Interim Analyses

To date, utilizing non-concurrent controls has only been discussed in platform trials without interim analyses in the literature. In this setting, it was shown that the regression model that adjusts for time by including the factor period as fixed effect leads to unbiased effect estimates and asymptotically controls the type I error rate regardless of the time trend pattern, if the time trend affects all arms in the trial equally and is additive on the model scale. However, in practice, most of the platform trials take advantage of the possibility to modify the trial design based on interim looks at the trial data collected so far. If interim analyses are included, the definition of the factor periods becomes data dependent and the number of periods to adjust for depends on previous interim results. Furthermore, due to early stopping the sample sizes in the different arms become outcome dependent, and therefore treatment effect estimates are no longer unbiased. This can affect the adjustment for time trends in the linear model, and the type I error rate might no longer be controlled. Adjusting for time in a data-independent manner might provide a solution to this issue. In particular, using calendar time intervals as a covariate or modelling time by means of splines, as proposed in this thesis, are examples of methods that do not depend on the course of the trial and might thus control the type I error rate even in settings with interim analyses.



Further Considerations regarding Mixed Models

In this thesis, we only focused on mixed models that use the time covariate as a random effect. As a further step, mixed models that include an interaction between treatment and time as a random effect, while keeping both covariates as fixed effects could be considered. Such models could relax the assumption of equal time trends across all arms, which is necessary for valid inference using the fixed effect model with period adjustment. Moreover, we only evaluated the performance of the mixed models in scenarios with a deterministic time trend. Scenarios where the time trend follows a random walk might be more suitable for emphasizing the characteristics of these models. Further investigation could also be done to describe for which time trend strengths the inflation of the type I

*Further research is needed
in this case to assess under
which circumstances
minimax and TIE
can be guaranteed.*

*however, if the
sample size for
treatment arms are modified
due to interim results,
effect estimates would be no longer unbiased.*

5.2. Future Research

error rate achieves its maximum when using mixed models.

Further Considerations regarding Spline Regression

Besides using B-splines to model time in the spline regression, one could consider more advanced smoothing methods, such as P-splines. P-splines combine regression on many evenly spaced B-splines and a discrete roughness penalty on their coefficients. The penalty ensures an appropriate trade-off between the fit to the data and the smoothness of the estimated curve. Unlike B-splines, P-splines do not involve explicit positioning of the knots. Instead, only one tuning parameter needs to be chosen, which determines the balance between fidelity to the data and smoothness. An optimal tuning parameter can be selected for instance using cross validation or based on Akaike's Information Criterion (AIC). The P-splines methodology has many useful extensions, such as adaptive smoothing, where the tuning parameter can vary along the data domain. In the case of platform trials, this would allow for different amount of smoothness of the estimated time trend function in different periods of time. Exploring P-splines and their properties in the context of non-concurrent controls provides an interesting future research topic.

Further Considerations regarding Randomization

So far, we have only considered block randomization and $1 : 1 : \dots : 1$ allocation ratio in each period to generate the data. Extending the work to cover also other allocation rates would provide further potential to propose tailored strategies for model-based adjustments according to the allocation. Moreover, considering more flexible randomization methods, such as response adaptive randomization, where non-concurrent control data would contribute to appropriately adjusting the allocation ratio in order to favor better performing treatment arms, would further increase the efficiency of the trial design.

→ future research/work on NCC package?
→ Different populations?

Bibliography

- [1] F. Bretz, F. Koenig, W. Brannath, E. Glimm, and M. Posch, “Adaptive designs for confirmatory clinical trials,” *Statistics in Medicine*, vol. 28, no. 8, pp. 1181–1217, 2009.
- [2] W. Brannath, F. Koenig, and P. Bauer, “Multiplicity and flexibility in clinical trials,” *Pharmaceutical statistics*, vol. 6, pp. 205–216, jul 2007.
- [3] E. L. Meyer, P. Mesenbrink, C. Dunger-Baldauf, H. J. Fülle, E. Glimm, Y. Li, M. Posch, and F. König, “The Evolution of Master Protocol Clinical Trial Designs: A Systematic Literature Review,” *Clinical Therapeutics*, vol. 42, no. 7, pp. 1330–1360, 2020.
- [4] J. Woodcock and L. M. LaVange, “Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both,” *New England Journal of Medicine*, vol. 377, pp. 62–70, jul 2017.
- [5] O. Collignon, C. Gartner, A. B. Haidich, R. James Hemmings, B. Hofner, F. Pétavy, M. Posch, K. Rantell, K. Roes, and A. Schiel, “Current Statistical Considerations and Regulatory Perspectives on the Planning of Confirmatory Basket, Umbrella, and Platform Trials,” *Clinical Pharmacology & Therapeutics*, vol. 107, pp. 1059–1067, may 2020.
- [6] O. Collignon, A. Schiel, C.-F. Burman, K. Rufibach, M. Posch, and F. Bretz, “Estimands and Complex Innovative Designs,” *Clinical Pharmacology & Therapeutics*, mar 2022.
- [7] L. E. Dodd, B. Freidlin, and E. L. Korn, “Platform Trials — Beware the Non-comparable Control Group,” *New England Journal of Medicine*, vol. 384, no. 16, pp. 1572–1573, 2021.
- [8] H. U. Burger, C. Gerlinger, C. Harbron, A. Koch, M. Posch, J. Rochon, and A. Schiel, “The use of external controls: To what extent can it currently be recommended?,” *Pharmaceutical Statistics*, no. January, pp. 1–15, 2021.
- [9] M. Bofill Roig, C. Burgwinkel, U. Garczarek, F. Koenig, M. Posch, Q. Nguyen, and K. Hees, “On the use of non-concurrent controls in platform trials: A scoping review,” nov 2022.
- [10] K. Viele, S. Berry, B. Neuenschwander, B. Amzal, F. Chen, N. Enas, B. Hobbs, J. G. Ibrahim, N. Kinnersley, S. Lindborg, S. Micallef, S. Roychoudhury, and L. Thompson,

Bibliography

- “Use of historical control data for assessing treatment effects in clinical trials.” *Pharmaceutical statistics*, vol. 13, no. 1, pp. 41–54, 2014.
- [11] F. Jiao, W. Tu, S. Jimenez, V. Crentsil, and Y.-F. Chen, “Utilizing shared internal control arms and historical information in small-sized platform clinical trials,” *Journal of biopharmaceutical statistics*, vol. 29, no. 5, pp. 845–859, 2019.
 - [12] H. Schmidli, D. A. Häring, M. Thomas, A. Cassidy, S. Weber, and F. Bretz, “Beyond randomized clinical trials: Use of external controls,” *Clinical Pharmacology & Therapeutics*, vol. 107, no. 4, pp. 806–816, 2020.
 - [13] A. Banbeta, J. van Rosmalen, D. Dejardin, and E. Lesaffre, “Modified power prior with multiple historical trials for binary endpoints,” *Statistics in Medicine*, vol. 38, pp. 1147–1169, mar 2019.
 - [14] B. P. Hobbs, B. P. Carlin, S. J. Mandrekar, and D. J. Sargent, “Hierarchical commensurate and power prior models for adaptive incorporation of historical information in clinical trials,” *Biometrics*, vol. 67, no. 3, pp. 1047–1056, 2011.
 - [15] H. Schmidli, S. Gsteiger, S. Roychoudhury, A. O’Hagan, D. Spiegelhalter, and B. Neuenschwander, “Robust meta-analytic-predictive priors in clinical trials with historical control information,” *Biometrics*, vol. 70, no. 4, pp. 1023–1032, 2014.
 - [16] K. M. Lee and J. Wason, “Including non-concurrent control patients in the analysis of platform trials: Is it worth it?,” *BMC Medical Research Methodology*, vol. 20, no. 1, pp. 1–12, 2020.
 - [17] M. Bofill Roig, P. Krotka, C.-F. Burman, E. Glimm, S. M. Gold, K. Hees, P. Jacko, F. Koenig, D. Magirr, P. Mesenbrink, *et al.*, “On model-based time trend adjustments in platform trials with non-concurrent controls,” *BMC medical research methodology*, vol. 22, no. 1, pp. 1–16, 2022.
 - [18] B. Consultants, *FACTS - Fixed and adaptive clinical trial simulator*, 2023. <https://www.berryconsultants.com/wp-content/uploads/2014/09/FACTS-Overview.pdf>.
 - [19] Cytel, *East*, 2023. <https://www.cytel.com/hubfs/0-2018/east/east.pdf>.
 - [20] W. JK, *Octopus - optimize clinical trials on platforms using simulation*, 2020. <https://github.com/kwathen/OCTOPUS>.
 - [21] T. Jaki, P. Pallmann, and D. Magirr, “The R package MAMS for designing multi-arm multi-stage clinical trials,” *Journal of Statistical Software*, vol. 88, no. 4, pp. 1–25, 2019.
 - [22] K. Anderson, *gsDesign: Group Sequential Design*, 2022. <https://CRAN.R-project.org/package=gsDesign>.

Bibliography

- [23] F. P. Gernot Wassmer, *rpact: Confirmatory Adaptive Clinical Trial Design and Analysis*, 2022. <https://CRAN.R-project.org/package=rpact>.
- [24] E. Meyer, *SIMPLE - SIMulating PLatform trials Efficiently*, 2022. <https://github.com/el-meyer/simple>.
- [25] B. R. Saville, D. A. Berry, N. S. Berry, K. Viele, and S. M. Berry, “The bayesian time machine: Accounting for temporal drift in multi-arm platform trials,” *Clinical Trials*, p. 17407745221112013, 2022.
- [26] M. Bofill Roig, F. König, E. Meyer, and M. Posch, “Commentary: Two approaches to analyze platform trials incorporating non-concurrent controls with a common assumption,” *Clinical Trials*, p. 17407745221112016, 2022.
- [27] I. C. Marschner and I. M. Schou, “Analysis of adaptive platform trials using a network approach,” *Clinical Trials*, p. 17407745221112001, 2022.
- [28] P. Krotka, K. Hees, P. Jacko, D. Magirr, M. Posch, and M. B. Roig, “NCC: An R-package for analysis and simulation of platform trials with non-concurrent controls,” 2023.
- [29] P. Krotka, M. Bofill Roig, K. Hees, P. Jacko, and D. Magirr, *NCC: Simulation and Analysis of Platform Trials with Non-Concurrent Controls*, 2023. <https://pavlakrotka.github.io/NCC/>, <https://github.com/pavlakrotka/NCC>.

A. Appendix

Include package manual and/or simulation code?