# 2. Methods

In this chapter, we first review the current methods for incorporating non-concurrent controls into the analysis of platform trials in Section 2.1. We 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 modelling 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 $k$ ($k = 1, \ldots, K$, ordered by entry time) and the control group by $k = 0$. Furthermore, we denote the periods the trial consists of by $s$ ($s = 1, \ldots, S$) and the calendar time units by $c$ ($c = 1, \ldots, C$). The total number of patients in the trial is given by $N$. The response for patient $j$ ($j = 1, \ldots, N$) 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.

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.

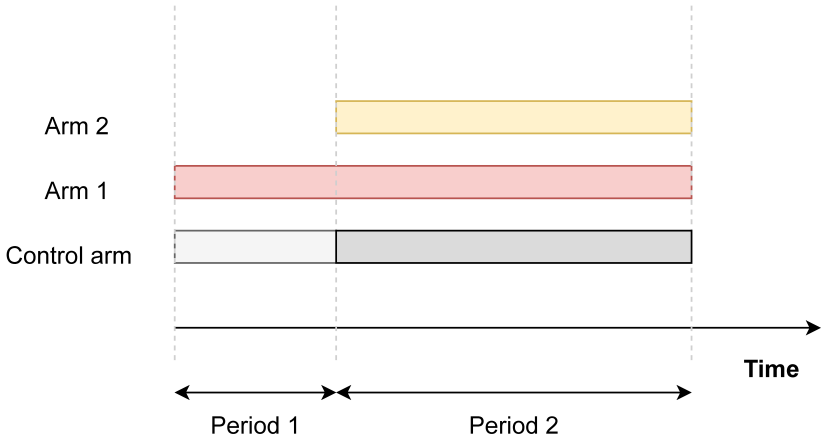


Figure 2.1.: Scheme of the platform trial considered in [16] and [17].

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:

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

$$y_j = \eta_0 + \sum_{k=1,2} \theta_k \cdot I(k_j = k) + \tau \cdot I(s_j = 2) + \varepsilon_j \tag{2.2}$$

where the model intercept is denoted by $\eta_0$ (in (2.2) this corresponds to the control response in the first period) and $\theta_k$ is the treatment effect for treatment $k$. The time effect is estimated by the parameters $\gamma$ and $\tau$. In (2.1), $\gamma$ represents the effect of continuous recruitment, while in (2.2) $\tau$ denotes the time effect between period 1 and 2. The residuals $\varepsilon_j$ are assumed to be normally distributed with mean 0 and variance $\sigma^2$ ($\varepsilon_j \sim \mathcal{N}(0, \sigma^2)$). 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.

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:

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

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 $\eta_0$ denotes the response of the control group at time of the analysis, $\theta_{k_j}$ is the effect of the treatment arm $k$ that patient $j$ was enrolled in, relative to control. For the parameters $\eta_0$ and $\theta_{k_j}$, normal prior distributions are assumed, with mean 0 and variances $\sigma^2_{\eta_0}$ and $\sigma^2_\theta$, respectively:

$$\eta_0 \sim \mathcal{N}(0, \sigma^2_{\eta_0})$$
$$\theta_{k_j} \sim \mathcal{N}(0, \sigma^2_\theta)$$

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

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:

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

where $\tau$ 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

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:

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

where $\boldsymbol{X}$ is a design matrix specifying the possible treatment contrasts in all periods the trial and $\boldsymbol{W}$ 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.

## 2.2. 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.

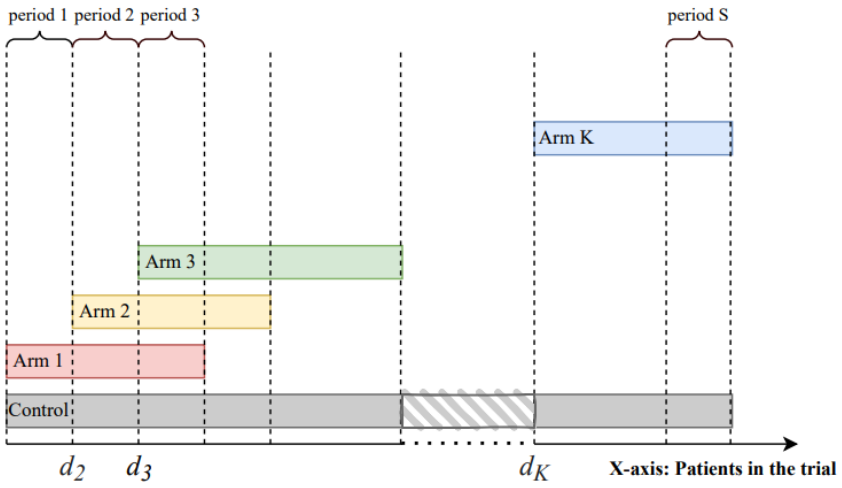


Figure 2.2.: Scheme of the considered general platform trial.

First, we divide the trial into periods, defined as time intervals bounded by adding or dropping experimental treatment arms. For each experimental treatment arm $k$ ($k \in \{1, \ldots, K\}$), $\mathbb{P}(k_j = k)$ is the probability of being allocated to this arm. This probability is strictly positive when the arm is active in the trial (i.e. open for randomization) and 0 before it enters and after it leaves the platform, defined as follows:

$$\mathbb{P}(k_j = k) = \begin{cases} \frac{1}{|\mathcal{K}_A(t)|+1} & \text{if } k \text{ active} \\ 0 & \text{if } k \text{ inactive} \end{cases}$$

where $\mathcal{K}_A(t)$ is the set of active experimental arms at time $t$.
We define the entry and exit times of the treatment arm $k$ by $t_k^{entry}$ and $t_k^{exit}$ such that:

$$k \in \mathcal{K}_A(t) \text{ if } t \in [t_k^{entry}, t_k^{exit}]$$

Denoting by $\mathbf{t}^{entry,exit} = \{t_1^{entry}, t_1^{exit}, t_2^{entry}, t_2^{exit}, \ldots t_K^{entry}, t_K^{exit}\}$ a vector containing the entry and exit times of all experimental arms, we define the end of a period $s$ by $t_s^{end}$, considering:

$$t_1^{end} = \min\{t \in \mathbf{t}^{entry,exit} \mid t > 0\}$$
$$t_s^{end} = \min\{t \in \mathbf{t}^{entry,exit} \mid t > t_{s-1}^{end}\} \text{ for } s \in \{2, \ldots, S\}$$

where $S$ is the total number of periods in the trial as before.

Finally, the time interval for a period $s$ is given by:

$$T_1^S = [0, t_1^{end}]$$
$$T_s^S = (t_{s-1}^{end}, t_s^{end}] \text{ for } s \in \{2, \ldots, S\}$$

The trial can also be divided into equidistant units of calendar time. Given the length of the calendar time interval $c_{length}$, the trial consists of $C = \min\{x \in \mathbb{N} \mid x \geq N/c_{length}\}$ such intervals. The time interval for a calendar time unit $c$ is then given by:

$$T_1^C = [0, c_{length}]$$
$$T_c^C = ((c-1) \cdot c_{length}, c \cdot c_{length}] \text{ for } c \in \{2, \ldots, C-1\}$$
$$T_C^C = ((C-1) \cdot c_{length}, t_K^{exit}] \text{ for } c = C$$

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 $\theta_M$ 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 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 $\mathcal{D}_M = \{(y_j, k_j, t_j), j = 1, ..., N \mid t_j \leq t_M^{exit}\}$. Note that also data from unfinished arms is included to the models. We summarize the notation in Table 2.1. 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 $t_M^{exit}$ 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.

| Notation | Definition |
|---|---|
| $K$ | number of experimental treatment arms |
| $k = 0, \ldots, K$ | arm indicator |
| $N$ | total number of patients in the trial |
| $j = 1, \ldots, N$ | patient index |
| $S$ | total number of periods |
| $s = 1, \ldots, S$ | period indicator |
| $C$ | total number of calendar time units |
| $c = 1, \ldots, C$ | calendar time unit indicator |
| $y_j$ | response of patient $j$ |
| $t_j$ | patient recruitment time of patient $j$ |
| $\mathcal{K}_A(t)$ | set of treatment arms active at time $t$ |
| $t_k^{entry}$ | entry time of treatment arm $k$ |
| $t_k^{exit}$ | exit time of treatment arm $k$ |
| $t_s^{end}$ | end time of period $s$ |
| $T_s^S$ | time interval of period $s$ |
| $T_c^C$ | time interval of calendar time unit $c$ |
| $\theta_k$ | treatment effect of treatment $k$ |
| $M$ | 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.

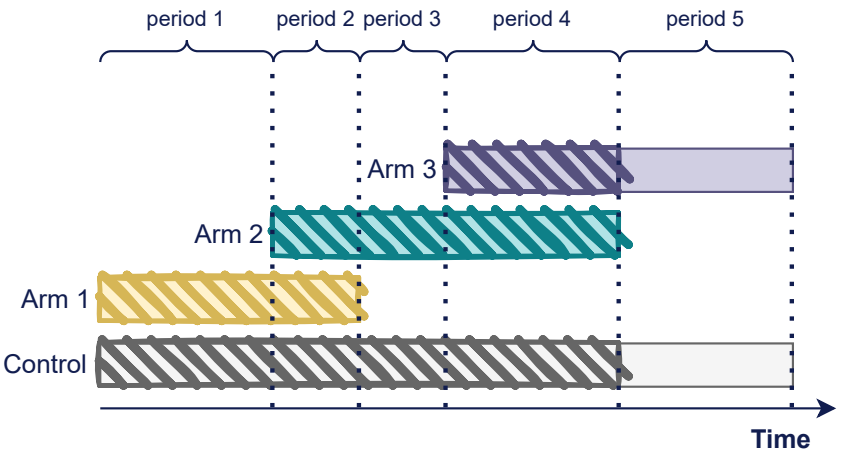


Figure 2.3.: Illustration of the data set $\mathcal{D}_2$. Data taken into account for the evaluation of the 2nd treatment arm are highlighted.

| 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 (2.7) |
| **Mixed-effect model with calendar time adjustment and autocorrelated random effects** | calendar time | random effect | Section 2.2.2 Equation (2.8) |
| **Spline regression model with knots according to periods** | period | polynomial spline | Section 2.2.3 Equation (2.10) |
| **Spline regression model with knots according to calendar times** | calendar time | polynomial spline | Section 2.2.3 Equation (2.10) |

Table 2.2.: Summary of the proposed models.

#### 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:

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

where $\eta_0$ is the response in the control arm in the first period; $\theta_k$ represents the effect of treatment $k$ compared to control for $k \in \mathcal{K}_M$, where $\mathcal{K}_M = \{\mathcal{K}_A(t) \mid t \in [0, t_M^{exit}\}$ is the set of treatments that were active in the trial during periods prior or up to $t_M^{exit}$; $\tau_s$ indicates the stepwise period effect between periods 1 and $s$ ($s = 2, \ldots, S_M$), where $S_M = \{s \mid t_M^{exit} \in T_s^S\}$ denotes the period, in which arm $M$ left the trial (i.e. the period in which $t_M^{exit}$ 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 model a constant time trend over each 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.

#### 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:

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

Here $\eta_0$ represents the control response in the first calendar time unit; $\theta_k$ 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. $\tau_c$ is the effect between calendar time units 1 and $c$ ($c = 2, \ldots, C_M$), where $C_M$ indicates the calendar time unit, in which arm $M$ left the trial.

The division of the trial into calendar times in 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, the time effect is modelled as constant in each unit and assumed 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.

### 2.2.2. Mixed Models

In models (2.5) and (2.6), time is considered 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:

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

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

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

where, $y_j$ and $\theta_k$ has the same interpretation as in the fixed effect models. The model intercept $\eta_0$ 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 $\sigma^2_{period}$:

$$\boldsymbol{u} \sim \mathcal{N}(0, \sigma^2_{period} \cdot I_{S_M \times S_M})$$

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

$$\boldsymbol{u} \sim \mathcal{N}(0, \sigma^2_{calendar} \cdot I_{C_M \times C_M})$$

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 $\varepsilon_j$, associated with the response of individual patient $j$ is assumed to be the same for all treatments:

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

The random effects, $u_s$ or $u_c$, and the residuals, $\varepsilon_j$, 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).

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 $\sigma^2_{period}$ and an AR(1) correlation structure:

$$\boldsymbol{u} \sim \mathcal{N}(0, \sigma^2_{period} \cdot \Sigma_{S_M \times S_M})$$

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

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

$$\boldsymbol{u} \sim \mathcal{N}(0, \sigma^2_{calendar} \cdot \Sigma_{C_M \times C_M})$$

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

The parameter $\phi$ denotes the correlation between two adjacent periods or calendar time units. Note that $\phi$ can range from -1 to 1 and the correlation of periods that are $w$ units apart is equal to $\phi^w$, 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:

$$\boldsymbol{\varepsilon} \sim \mathcal{N}(0, \sigma^2 \cdot I_{N \times N}) \tag{2.9}$$

### 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:

$$y_j = \eta_0 + \sum_{k \in \mathcal{K}_M} \theta_k \cdot I(k_j = k) + f(t_j) + \varepsilon_j \tag{2.10}$$

where $y_j$, $\eta_0$ and $\theta_k$ 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 $f(t_j)$ of the patient entry time $t_j$, which in our case also indicates their index ($t_j = j$).

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 entire spline is continuously differentiable up to the $(q-1)$th derivative. In our case, the knots are placed within the range of the patient entry times $t_j$. To define a B-spline function, we first define the knot sequence

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

where the $Z$ knots in the set $\{\zeta_{q+2}, \ldots, \zeta_{q+Z+1}\}$ are called *inner knots*, while $\zeta_{q+1}$ and $\zeta_{q+Z+2}$ are referred to as *boundary knots*. The additional knots $\{\zeta_1, \ldots, \zeta_q\}$, as well as $\{\zeta_{q+Z+3}, \ldots, \zeta_{Z+2q+2}\}$ 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 $f(t_j)$ can then be represented by a set of basis functions $B_i^q(t_j)$ as follows:

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

where $\beta_i$ are the associated regression coefficients and the functions $B_i^q(t_j)$ are defined using the Cox-de Boor formula, recursive in $q$, as follows:

$$B_i^q(t_j) = \frac{t_j - \zeta_i}{\zeta_{i+q} - \zeta_i} B_i^{q-1}(t_j) + \frac{\zeta_{i+q+1} - t_j}{\zeta_{i+q+1} - \zeta_{i+1}} B_{i+1}^{q-1}(t_j), \qquad i = 1, \ldots, q+Z+1$$

with

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

and

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

For the positions of the inner knots $\{\zeta_{q+2}, \ldots, \zeta_{q+Z+1}\}$, 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 $s = 2, \ldots, S$, 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 $\zeta_{q+1}$

and $\zeta_{q+K+2}$ 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.