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Nonconcurrent Controls in Platform Trials: Can We Borrow Their Concurrent Observation Data?

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ABSTRACT

Adaptive platform trials (APTs) offer an innovative approach to studying multiple therapeutic interventions more efficiently through flexible features such as adding and dropping interventions as evidence emerges, creating a seamless process that avoids enrollment disruption. The benefits and practical challenges of implementing APTs have been widely discussed in the literature; however, less consideration has been given to how to use the nonconcurrent control (NCC) data (i.e., the data generated by patients recruited in the control arm before a new treatment is added) when the outcome of interest is a time to event endpoint. Including the NCC can increase the power of the trial. However, due to the omnipresent change of standard care over time, complete borrowing of the NCC survival data may lead to some bias in the estimation. In this article, we propose an alternative approach to borrow the concurrent observation part of the NCC data by left truncation using a simple decision-making flowchart, which can reduce the bias due to the change of standard care under certain assumptions. Then, the restricted mean survival time (RMST), estimated by the Kaplan-Meier method, is used to compare the treatment versus the pooled control group. We present two simulation studies to illustrate the performance of the decision-making flowchart method under different scenarios. We advocate researchers and drug developers to apply and validate this simple approach in practice.

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Kaplan-Meier method; Master protocol; Nonconcurrent control; Platform trial; Restricted mean survival time

1. Introduction

Traditionally, drug development follows the "one drug for one disease" paradigm, which focuses on a single treatment for one target disease at once. Despite being used extensively, this paradigm has long been criticized with its high costs and long time (Berry, Connor, and Lewis 2015). Due to these limitations, innovative trial designs such as "master protocol" (intended to simultaneously evaluate more than one investigational drug and/or more than one disease type within the same overall trial structure) are gaining attention in recent years (Woodcock and LaVange 2017). The platform trial is a type of randomized master protocol trial that allow the simultaneous comparison of multiple intervention groups against a single common control group based on a pre-specified interim analysis plan to improve efficiency. It allows an investigator to study multiple treatments in a perpetual manner using a single overarching master protocol with the new interventions entering and dropping the trial by some predetermined criteria (Angus et al. 2019). The platform trials have the advantages in creating an efficient trial infrastructure that can help address critical questions as the new interventions and the clinical evidence evolve.

The ability to add new treatment arms in a platform trial raises the question of how to use all available control data (Cohen et al. 2015; Saville and Berry 2016; Ventz et al. 2018; Lee, Wason, and Stallard 2019; Lee et al. 2021; Lu et al. 2021; Sridhara et al. 2022;). There have been ongoing debates among researchers on whether and how the nonconcurrent control (NCC) information can be used in platform trials or in what situation the usage of NCC is appropriate. Here the concurrent control (CC) and the NCC groups refer to the patients in the control arm who are randomized in the concurrent/nonconcurrent time period with the patients randomized in the treatment group(s) of interest (Lee and Wason 2020). The use of nonconcurrent control data is controversial because the population drift, calendar time bias, or the change in the standard of care may cause bias in the estimation (Dodd, Freidlin, and Korn 2021; Park et al. 2022; Sridhara et al. 2022). Therefore, the FDA for registrational studies and some researchers advocate only using the CC data to estimate the treatment effect (Wason et al. 2016; Ventz et al. 2018; Angus et al. 2019; Lee, Wason, and Stallard 2019; Collignon et al. 2020; Collignon 2022; Sridhara et al. 2022) advised using NCC data in some early-phase trials or academic trials where the control of Type I error is more flexible. Others mentioned the possibility of including the NCC data after accounting for the possible time trend (Saville and Berry 2016; Woodcock and LaVange 2017; Butler et al. 2018; Park et al. 2020; Lee et al. 2021). Some parametric methods for modeling the trend in NCC group are proposed recently (Lee, Wason, and Stallard 2019; Lee and Wason 2020; Roig et al. 2021; Wang et al. 2023). Lee and Wason (2020) considered a linear regression model with a time-related covariate to account for the

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time trend. Roig et al. investigated the step function model and its ability to control the Type 1 error rate. Wang et al. proposed a Bayesian approach in order to incorporate the NCC data with "down weighting" according to clinical judgments. Roychoudhury et al. also propose to incorporate historical information for a control arm with a Bayesian method. Normal dynamic linear model (NDLM) proposed by Berry et al. has been implemented in multiple well-recognized platform trials such as the randomized embedded multi-factorial adaptive platform trial for community-acquired pneumonia (REMAP-CAP) and the platform randomized trial of treatments in the community for epidemic and pandemic illnesses (PRINCIPLE) (Angus et al. 2020a; Collignon et al. 2021).

It is worth mentioning that in a forum organized by the ASA Biopharmaceutical Statistical Methods in Oncology Scientific Working Group in coordination with the U.S. Food and Drug Administration (FDA) Oncology Center of Excellence (Sridhara et al. 2022), the panelists from global regulatory as well as academia and industry representatives came to a consensus to recommend only include the concurrent randomized control data for confirmatory trials with registration intent, while analysis including all controls may be served as a sensitivity analysis. The recent FDA guidance on COVID-19 related master protocol trials also provided consistent recommendations to conduct statistical analyses for a given investigational drug on comparisons against only those control arm patients who were concurrently randomized with the investigational drug (COVID-1919 2021). On the other hand, in rare diseases settings where conducting a large platform trial is challenging, it is more acceptable to use all available control arm data by including nonconcurrent control after scrutiny of the heterogeneity of the control arm data over time with appropriate statistical models taking account of potential bias (Lu et al. 2021; Sridhara et al. 2022).

This article focuses on using NCC data to analyze time to event endpoint in the context of platform trials. In light of the various concerns of using the complete NCC data in platform trials, we propose an innovative approach of borrowing the concurrent observation time of the NCC patients in the platform trials to alleviate some of the concerns, in particular, the noncomparability between NCC and CC due the change of the standard of care. As illustrated in the left panel of Figure 1, we define the concurrent observation time for the NCC control as the time interval between the time of first patient randomized to the "new" treatment arm and the study end date for the "new"

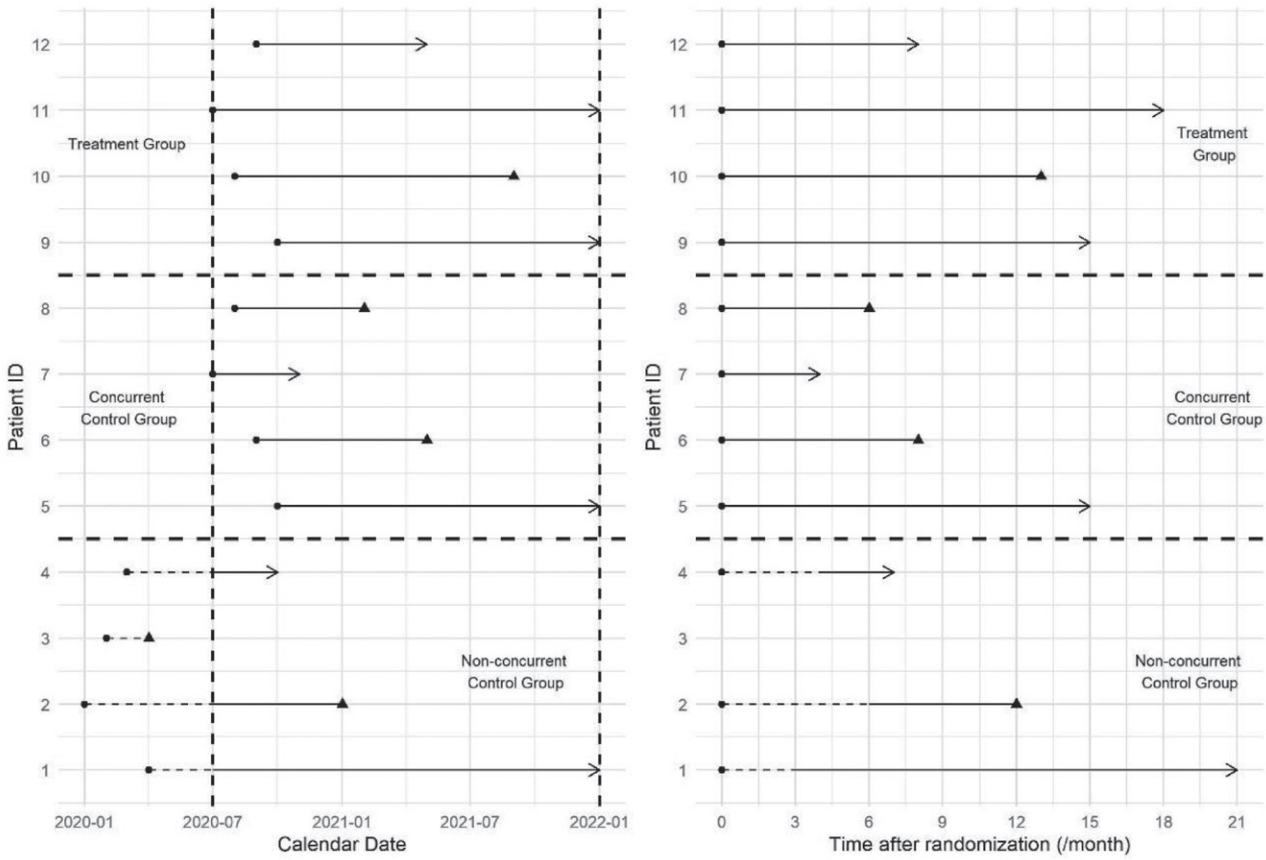

Figure 1. Illustration on the definition of (left panel) and how to use concurrent observation time (right panel) from nonconcurrent controls. The left panel uses the calendar date, while the right panel uses time after randomization as x-axis. The first vertical dashed line indicates the time of first patient randomized, the second dashed line indicate the study end date for the "new" intervention arm. The concurrent observation time is the interval between the two dashed lines. The circle denotes the entering time of each individual in the platform trial and the triangle represents the event time. The right arrow indicates right censoring due to the end of study or lost to follow-up. Patient 1–4 is from the nonconcurrent control group which were randomized before the entering of the new treatment. Patient 9–12 is from the new treatment group and patient 5–8 is from the concurrent control group. The dashed horizontal lines for patient 1–4 in the left panel denotes left truncated survival time which equals to the time of each NCC patient spent before the entering of the new treatment. In the right panel of Figure 1 for the survival data of each patient, the dashed horizontal lines for patient 1, 2, and 4 indicate the left truncation period, in which the patient is not in the risk set. Note that, the data from patient 3 is not included in the right panel due to left truncation.

treatment arm. This definition can incorporate a lag period if it is necessary and clinically supported. Thus, the survival time of the NCC patients is composed of nonconcurrent observation time (before the new intervention entering the trial) and concurrent observation time (after the new intervention entering the trial). To enhance existing approaches on borrowing the NCC data (typically as a dichotomized decision of whether to borrow the whole NCC data or not), we provide a new perspective by asking a different question: which part of the NCC data can be borrowed under what scenarios? Through the decision-making flowchart, we trisect the decisions into: (a) use the entire NCC data; (b) use only the concurrent observation time of the NCC data, and (c) not use any NCC data. The proposed decision-making flowchart considers the efficiency and accuracy trade-offs: it borrows as much information as we can and in the meanwhile minimizes the influence of the change of standard care in the control group. We will elaborate this further in the later sessions.

Section 2 explains the proposed method in detail and introduces the restricted mean survival time (RMST). In Section 3, we use two simulations, each under three scenarios to evaluate the benefit of borrowing concurrent observation time data from NCC patients. Section 4 presents a brief discussion.

2. Statistical Methods

2.1. The Concurrent Observation Time Data for the NCC Group

To illustrate how to borrow survival data in the concurrent observation time of nonconcurrent control patients, without loss of generality, we consider a platform trial with two treatment arms A, B and a control arm C. Treatment A and control C start at the beginning of the trial and Treatment B enters the trial at time t_0, which is the time that the first patient randomized for treatment B, after the recruitment of treatment A. When the evaluation of Treatment B is of interest, the control group can be divided into a nonconcurrent control group (patients recruited before treatment B starts) and a concurrent control group (patients randomized simultaneously with treatment B).

For the NCC group, following the definition of concurrent observation time in NCC group detailed in Section 1 and illustrated in Figure 1, we propose to borrow the information of concurrent observation time under specific suitable scenarios. We achieve this by modifying the risk set to be the collection of patients who are in the concurrent observation period. In other words, patients are only considered at risk when they are in the concurrent observation period. This method ignores the information generated in the nonconcurrent period, thus, is equivalent to left truncating the survival data with the truncation time equaling to the time that the patient spends before entering the concurrent observation period. If patient i in the NCC group entered the trial at time t_i, then the left truncation time of individual i will be $L_i = t_0 - t_i$ if the individual successfully entered the concurrent time period. Note that if the individual failed to enter the concurrent time period, then this patient's information will not be used in our proposed method due to the left truncation. The borrowing of the NCC group concurrent observation time data allows NCC patients to change the standard of care while on study such that NCC concurrent observation time and CC share the same standard of care.

2.2. Using the Nonconcurrent Control Data in a Platform Trial

The concurrent observation time of the NCC group has the same calendar period as the CC group and the treatment group. Thus, we assume that NCC patients in their concurrent observation period use the same standard of care (SoC) as the CC patients. With this assumption, using the NCC group concurrent observation data can reduce the influence of the change in the standard of care (SoC) in the NCC group. However, we acknowledge that the validity of this assumption depends on the specific disease, enrollment, and development landscape. Besides, if the population characteristics are different between the NCC group and the CC group (population drift) or the patients' experience in the nonconcurrent period will influence their hazards in the concurrent period, the NCC patients in their concurrent observation time may not have the same hazard as the counterpart of CC patients. In these cases, using the NCC concurrent observation time data may cause bias when estimating the treatment effect. On the other hand, there may not be significant changes in the SoC for some diseases over a long period of time, which may justify borrowing the entire NCC group data. In such situations, only borrowing the concurrent observation time data from the NCC group may not generate the optimal results for the treatment effect.

We propose a general decision-making flowchart (Figure 2) to reduce bias and increase precision when using the NCC data in a platform trial. The first step is to decide whether we can borrow the entire NCC group data. In this step, both clinical and statistical evaluations need to be conducted. For the clinical evaluation, trialists need to consider whether there are notable changes in the standard of care, patient population, enrollment pattern, inclusion/exclusion criteria, disease characteristics, the assessment of endpoints, and implications on whether we can borrow the entire (or part of) NCC group data. For instance, it is generally not recommended to use NCC group data for fast-changing infectious diseases like COVID-19 with various variants over time. For the statistical evaluation, we propose to compare the CC group and the NCC group to decide whether there is a nontrivial statistical difference between the two groups. As a general rule, we consider that the two groups are different (e.g., based on RMST difference) is statistically significant or the difference is medically meaningful. For instance if the restricted mean survival time (RSMT) difference is larger than 10% of the RMST of CC group given the same restricted time τ (see next section for RMST). Researchers and drug developers can change this decision rule based on specific trial requirements, for example, change the 10% different to be 5%, 15%, or even 20%.Understanding the practical challenges of recruitment and the rarity of the disease population may contextualize the similarity assessment from both clinical and statistical sides. If both the clinical and statistical assessments indicate no difference between the NCC group and the CC group, we can simply borrow the entire NCC group data and compare the pooled control group with the treatment group.

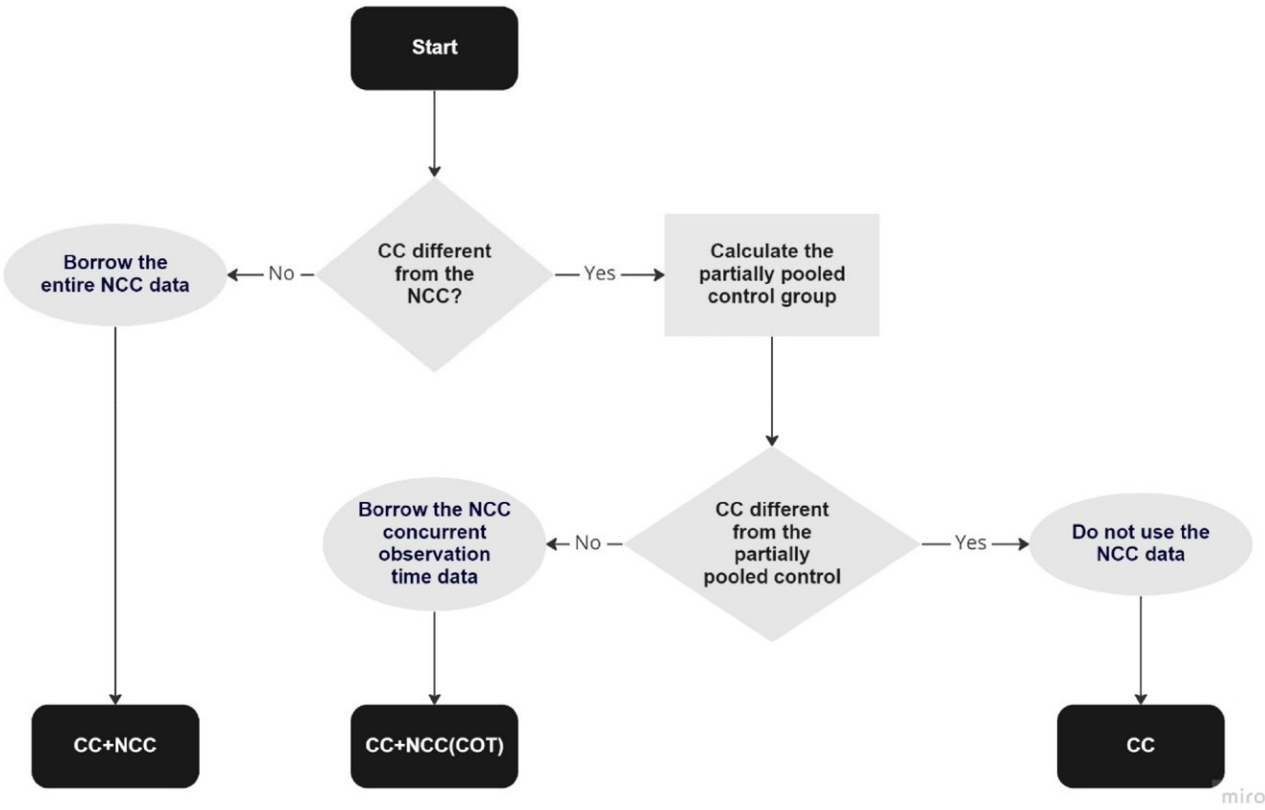

Figure 2. The decision-making flowchart for using the NCC group data in the platform trial.

If the decision is to not borrow the entire NCC group data, we then proceed to the second step to decide if the concurrent observation time data can be borrowed from the NCC group. Similar to the first stage, this decision is made with careful consideration from both clinical and statistical perspectives. The clinical perspective is fundamental in the evaluation and the considerations are similar to the first step, except the assessment of SoC because only borrowing the concurrent observation time data from the NCC group can account for the change of SoC (see discussion section when the NCC group and CC group do not implement the same SoC in the concurrent observation period). All other conditions need to be evaluated before borrowing the concurrent observation time data from the NCC group. For the statistical perspective, we pool the concurrent observation time data in the NCC group with the CC group data to form a "partially" pooled control group. Then, we can compare this "partially" pooled control group with the CC group using the same criterion to see whether there is nontrivial difference between them (using the same criteria as before). Note that we do not directly compare the NCC concurrent observation time data with the CC data, because the survival estimated from the NCC concurrent observation time data can be unstable due to left truncation and small number of subjects in the risk sets at the beginning of the comparison. Since the "partially" pooled control group includes the CC group, we can use the bootstrap method to evaluate the uncertainty of their difference. If we decide not to borrow any data, we then only use the CC group data to estimate the treatment effect. Otherwise, we can borrow the concurrent observation time data from the NCC group and use the partially pooled group to estimate the treatment effect.

2.3. Restricted Mean Survival Time (RMST)

Once we borrow the most appropriate part of the NCC data, we can construct the control group and calculate the treatment effect by comparing it with the treatment group. In this article, we use the restricted mean survival time (RMST) to summarize the difference of the overall survival for the treatment and the control groups. Liu et al. (2023) proposed to borrow the concurrent observation time data in the NCC group and used the Cox proportional hazard model for the data analysis. They used simulated example data to illustrate the concept, but did not evaluate the performance using simulation studies. The RMST is a model-free measurement which summarizes the overall performance of the survival curve up to a pre-specified time. Compared with the hazard ratio (HR) estimated in the Cox proportional hazard (PH) model, the RMST has a favorable clinical interpretation. The advantages of RMST have been discussed thoroughly in many literatures (Royston and Parmar 2011; Royston and Parmar 2013; Uno et al. 2014; Uno et al. 2015; A'Hern 2016; Zhao et al. 2016; Trinquart et al. 2016; Huang and Kuan 2018; Luo, Huang, and Quan 2019; Messori et al. 2020; Freidlin, Hu, and Korn 2021; Huang and Tian 2022). First, the estimation of RMST is model-free and does not rely on the proportional hazard assumption. Thus, RMST is more flexible and can be applied when the proportional hazard model does not hold (Uno et al. 2015). Second, RMST is easy to interpret from a clinical perspective compared with HR (e.g., the magnitude of the HR alone cannot be used to explain the magnitude of the relative risk (Sutradhar and Austin 2018)), especially when the PH assumption is violated. The increase in one year of RMST

indicates an one-year gain of expected life associated with the treatment (Trinquart et al. 2016). Moreover, RMST can be more efficient than the HR when the number of events is small. The RMST-based measurements can produce narrower confidence interval regardless of the validity of the proportional hazard assumption, especially in the noninferiority trials (Trinquart et al. 2016; Freidlin, Hu, and Korn 2021).

RMST is defined as the population mean of time to event limited to some pre-defined restricted time τ (Irwin 1949; Royston and Parmar 2013; Uno et al. 2014). Let random variable X be the survival time, then

$$\text{RMST } \mu_\tau = \int_0^\tau S(t)dt.$$

Where $S(t) = \Pr(X > t)$ is the survival function. Therefore, RMST can be calculated as the area under the survival curve $S(t)$ limited between $t = 0$ and $t = \tau$ (Royston and Parmar 2013). The survival curve $S(t)$ can be estimated nonparametrically using the Kaplan-Meier estimator (Klein and Moeschberger 2003) as

$$\hat{S}_{KM}(t) = \begin{cases} 1, & t < t_1' \\ \prod_{t_i' \le t}\left[1 - \frac{d_i}{Y_i}\right], & t_1' \le t \end{cases}$$

where t_i' is the distinct event time point of $\{t_1, \ldots, t_n\}$ with $t_1' < t_2' < \cdots < t_k'$, k be the number of distinct event time points, d_i is the number of events at time point t_i', Y_i is the number of patients at risk at time point t_i'. Note that, for left truncated and right censored data $(L_i, T_i, \delta_i, C_i)$ with L_i be the left truncation time, $T_i = \min(X_i, C_i)$ be the observed time, $\delta_i = I(x_i \le C_i)$ be the indicator function of right censoring and C_i be the right censoring time, Y_i is the number of subjects with $L_l \le t_i \le T_l (0 < l \le k$ Klein and Moeschberger (2003).

Another way of estimating the survival function is the Nelson-Aalen estimator which through the cumulative hazard function $H(t) = -\log S(t)$. Using the same notation, the Nelson-Aalen estimator of $H(t)$ can be expressed as

$$\hat{H}_{NA}(t) = \sum_{t_i' \le t} \frac{d_i}{Y_i}.$$

Then the survival function can be obtained by

$$\hat{S}_{NA}(t) = \exp(-\hat{H}_{NA}(t)).$$

RMST can be calculated as the area under the estimated survival curve for $t \le \tau$,

$$\widehat{\mu}_\tau = \int_0^\tau \hat{S}(t)\, dt = \sum_{t_i' \le \tau} \left(t_i' - t_{i-1}'\right) \hat{S}\left(t_{i-1}'\right).$$

The variance of RMST estimator can be calculated by plug in the Greenwood variance estimator of the survival probability in the generalization of Meier's variance estimator:

$$\hat{V}[\widehat{\mu}_\tau] = \sum_{t_i' \le \tau} \left[\int_{t_i'}^\tau \hat{S}(t)\, dt\right]^2 \frac{d_i}{Y_i(Y_i - d_i)}.$$

See more detailed discussion on the variance estimation (Klein and Moeschberger 2003; Zhao et al. 2016; Hasegawa et al. 2020; Nemes, Bülow, and Gustavsson 2020; Tian et al. 2020). Then the $100(1-\alpha)\%$ confidence interval can be constructed as $\widehat{\mu}_\tau \pm Z_{1-\alpha/2}\sqrt{\hat{V}[\widehat{\mu}_\tau]}$ (Klein and Moeschberger 2003).

3. Simulations

To illustrate the performance of our proposed decision-making flowchart, we present two simulation studies with different conditions. We evaluate four different methods of using the NCC control data in the platform trial. The first method uses the entire data of the NCC group to form pooled control group along with the CC group. The second method borrows the concurrent observation time data from the NCC group along to form partially pooled control group with the CC group. The third method only uses the CC group data. The last method uses the decision-making flowchart introduced in Section 2 to decide how to use the NCC data. Since it is not possible to assess similarity from a clinical perspective in the simulation, the decision is based solely on the statistical differences observed in the simulation study.

Assume the entering time of the new treatment is $t_0 = 6$ months. The NCC group is recruited through the time $[0, t_0]$ uniformly. The CC group and the new treatment group are recruited through $t_0 = 6$ to $t_1 = 9$. The maximum follow-up time is set to be $t_{\max} = 24$ month. In order to reflect the effect of trend (drift) in the NCC group, the hazard functions of the NCC group in the nonconcurrent time period (before the new treatment entering time t_0) and the concurrent time period (after t_0) are assumed to be different (proportional to a constant e^{β_t}). This is equivalent to viewing the hazard of a NCC patient follows a time-dependent Cox model (Austin 2012). Let t_i^c be the left truncation time of subject i which equals to the time that subject i is in the nonconcurrent period (the dashed horizontal line for each patient in Figure 1), and $I(\cdot)$ be the indicator function with $I\left(t \ge t_i^c\right) = 1$ for $t \ge t_i^c$ and $I\left(t \ge t_i^c\right) = 0$ for $t < t_i^c$. Thus, the hazard function of individual i in the NCC group is

$$h(t) = h_0(t)\exp(\beta_t I(t \ge t_i^c)).$$

In each simulation condition, we simulate the survival data according to three types of distributions, the exponential distribution $h_0(t) = \lambda$ with $\lambda = 0.3$, the Weibull distribution with increasing hazard $h_0(t) = \lambda\nu t^{\nu-1}$ where $\lambda = 0.25$, $\nu = 1.2$, and the Weibull distribution with decreasing hazard $h_0(t) = \lambda\nu t^{\nu-1}$ where $\lambda = 0.25, \nu = 0.9$. We assume $\beta_t = -0.8$ for the first simulation condition, and $\beta_t = -0.3$ for the second simulation condition which makes the concurrent time period has lower hazard (due to the improvement of standard of care) compared with the nonconcurrent time period. The sample size of each group is set to be 100 in order to mimic the scenario where the trial has relatively small sample size (such as the trial for rare disease) and the parameters are chosen to ensure sufficient number of events in the follow-up time.

For all three distributions, we present the average of the estimated RMST difference between the treatment group and the control group for each method. The bias of the RMST difference is calculated with respect to the true RMST difference between the treatment group and the CC group which is obtained by the 100,000 Monte Carlo sampling method. Except for the bias, we also calculate the mean squared error (MSE) for each method. For the estimated 95% confidence interval of the RMST difference, we compare its average length and coverage probability (i.e., the proportion of times that the estimated 95% CI contains the true RMST difference).

The first simulation condition assumes there is no population drift (i.e., patients in the CC group and the NCC group are similar) but there is change of the standard of care. Thus, the hazard functions of the CC group and the NCC group concurrent observation time are assumed to be the same, but different from the NCC group noncurrent observation time. It further assumes the hazard function of the new added treatment $h^T(t)$ is smaller than the CC control group, $h^T(t) = \beta_e \times h(t)$ where β_e is 0.2. See Figure 3 for the illustration of the individual hazard function. Due to the different randomized time, patients from the NCC group may experience different time in the noncurrent period before they enter the concurrent time period (i.e., receiving a new SoC). As an illustration, we plot the hazard function for patients who are randomized at calendar time $t = 0$ (red lines) and for patients who are randomized at $t = 3$ (red dashed lines).

The results for the first simulation condition are shown in Tables 1 and 2. Due to the change of standard of care, there is a difference between the NCC and CC groups. Thus, the method for using the entire NCC data has large bias and small coverage probability. However, using the NCC concurrent observation time data along with the CC data has nearly no bias and coverage rate close to 95% which show that it eliminates the influence of the change of standard of care. It also has shorter confidence interval compared with the results only using the CC data. Using the flowchart decision-making rule also has very small bias with coverage rate close to 95%, which is very close to the result of using the NCC concurrent observation time along with the CC group. We can also see that the flowchart method has larger mean squared error (MSE) compared with the NCC concurrent observation time data, since it occasionally excludes the entire NCC group data. As shown in Table 2, the decision-making flowchart (using both statistical significance at level $\alpha = 0.05$ and medical meaningful of 10% RMST change) can detect the difference between the NCC and the CC for over 90% of the times. For those cases that there is nontrivial difference between the CC and the NCC, only about 5% of the partially pooled group is different from the CC group (which is the Type-I error). Therefore, most of the decision is to borrow the NCC group concurrent observation time data, making these two results very close.

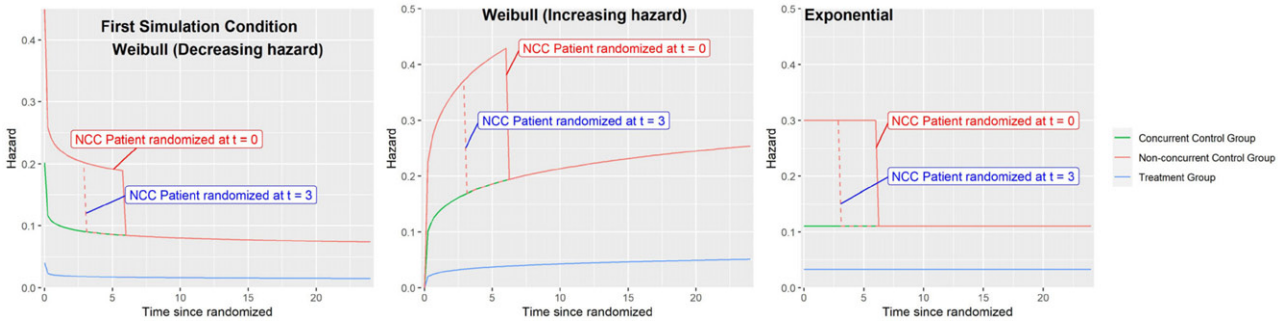

Figure 3. Individual hazard function for the first simulation condition, where we assume there is a change of the SoC in the concurrent period but no population drift (so that the hazard function for the NCC group is the same as the CC group in the concurrent observation time). Depending on the randomization time, patients from the NCC group may experience different time in the nonconcurrent period before they witch to the concurrent time. As an illustration, the red line is the hazard function for patients randomized at time $t = 0$ where they switch to the concurrent period after 6 months. The red dashed line indicates the hazard function for patients randomized at time $t = 3$ where they enter the concurrent observation period after 3 months.

Table 1. Simulation results for the first simulation condition which assume the treatment group has better performance compared with the control group.

Control group	Exponential		Weibull (decreasing hazard)		Weibull (increasing hazard)	
	RMST difference (bias) (MSE)	95%CI coverage (CI length)	RMST difference (bias) (MSE)	95%CI coverage (CI length)	RMST difference (bias) (MSE)	95%CI coverage (CI length)
CC + NCC	6.798 (−0.888) (1.117)	64.7% (1.128)	5.877 (−0.876) (1.165)	66.9% (1.168)	6.871 (−0.759) (0.860)	71.5% (1.081)
CC + NCC(COT*)	5.890 (0.020) (0.388)	95.1% (1.238)	4.907 (0.094) (0.469)	93.7% (1.294)	6.118 (−0.005) (0.326)	95.7% (1.159)
CC	5.905 (0.005) (0.463)	94.7% (1.309)	4.926 (0.075) (0.551)	92.9% (1.332)	6.137 (−0.025) (0.382)	95.6% (1.227)
Flowchart	5.908 (0.001) (0.424)	93.7% (1.237)	4.946 (0.055) (0.509)	92% (1.286)	6.133 (−0.021) (0.357)	94.7% (1.160)

NOTE: The four rows represent four different methods to use the NCC data. The first method uses the entire NCC group data. The second method uses the NCC but concurrent observation time data. The third method uses only the CC group data. The last method uses the decision-making flowchart proposed in Section 2. We simulate survival data according to three different distributions, the exponential distribution, the Weibull distribution with increasing hazard and the Weibull distribution with decreasing hazard. For each simulated data, we calculate the estimated RMST difference compared with the treatment group, its bias (the truth is calculated using 100,000 times Monte Carlo method) and mean squared error. The table also provides the number of times that the estimated 95% CI covers the true value and the average length of the 95% CI.
The true RMST difference is calculated through 100,000 Monte Carlo method.
NCC (COT): nonconcurrent control group in their concurrent observation time.

The second set of simulations assumes there is some population drift (i.e., patients in the CC group and the NCC group are different) and the standard of care is also shifted (so the NCC group and CC group will not have the same hazard function even in the concurrent observation period). Specifically, we assume that the treatment is no better than the control, that is, the treatment group and the CC group have the same hazard function. However, due to population drift, the NCC group is assumed to have a much higher hazard, (i.e., $h^{NCC}(t) = 2.5 \times h(t) = 2.5 \times h_0(t)\exp(\beta_t I(t \geq t_i^c))$ where $\beta_t = -0.3$) in the concurrent observation time. The other settings are assumed to be the same as the previous simulation. See Figure 4 for the illustration of different hazard functions. Since the population characteristics for the NCC group are different from the CC group, the use of NCC concurrent observation time data may cause bias in the estimation of the treatment effect. The results for the second simulation are shown in Tables 3 and 4. The true RMST difference is 0 (because there is no difference between the CC and treatment groups). We can see that both the entire NCC data and the NCC concurrent observation time data have large bias and small coverage rates. However, using the flowchart decision-making rule has a very small bias and the coverage rate close to 95%. It also has smaller MSE compared with the method using NCC data. That is because, as seen in Table 4, the flowchart decision rule detects a difference between the CC group and the partially pooled control group most of the times, thus, leading to only use the CC for comparison. Therefore, the result based on the flowchart decision rule is very close to that of only using the CC data.

Table 2. The decision-making flowchart results for the first simulation condition.

	Exponential	Weibull (decreasing hazard)	Weibull (increasing hazard)
CC different with NCC	95.9%	93.4%	95.5%
CC different with the partially pooled control (CC+ NCC COT)	5.1%	4.9%	5.7%

NOTE: For each simulated distribution, the first row is the proportion of case that the CC group is significantly different from the NCC group (either the difference is statistically significant at level $\alpha = 0.05$ or clinically significant of 10% RMST change). the second row is the proportion of cases that the CC group is different from the partially pooled control.
NCC (COT): nonconcurrent control group in their concurrent observation time.

4. Discussion

In this article, a decision-making flowchart of borrowing information from the nonconcurrent control data in the platform trial is proposed. Instead of borrowing the nonconcurrent control data over the entire time of the study by assuming some parametric models to eliminate the influence of the time trend in nonconcurrent control data, the proposed method focused on the possibility of borrowing the nonconcurrent control patients but only concurrent observation time data. This method does not require fitting any parametric models thus are robust to parametric model misspecification. Another apparent advantage of borrowing the NCC concurrent time rather than the entire time period from NCC is that in cases when the standard medical practices change over time, the NCC concurrent observation time being borrowed would reflect the survival under the concurrent standard medical practices as the CC group, while the survival time in the NCC group under different medical practices will not be borrowed.

On the other hand, to borrow the NCC group concurrent observation time, we need to assume that the hazard function for the concurrent observation time of NCC subjects is the same as the hazard function of the concurrent control patients. In other words, we need to assume: (a) the NCC patients take the same SoC as the CC patients in their concurrent observation time. Sometime, the NCC patients may not change their SoC even if the SoC is updated, if they are continuing to respond to their initial treatment. In this case, the NCC patients and CC patients can take different SoC during the concurrent observation period. Practically, the time point of left truncation could be set flexibly such that trialists can consider borrowing the period from NCC starting at a different time rather than the beginning of the concurrent observation time. For an example, the borrowing can be from the concurrent SoC period when the patients from the NCC group receives the same SoC as the patients from the CC group. The left-truncation time for the NCC patients would thus be the calendar time when they actually receive the concurrent SoC instead of the concurrent period time, which could be potentially earlier (or later) than the NCC concurrent observation time. However, such practice needs to be scrutinized with careful clinical evaluations. Another challenge of such a practice is, changing of SoC usually

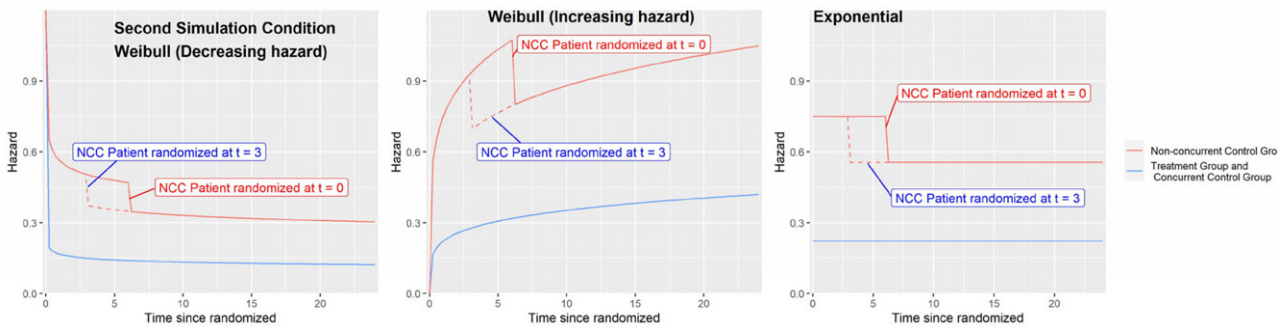

Figure 4. Individual hazard function for the first simulation condition, where we assume there is a change of the SoC in the concurrent period and a population drift (so that the hazard function for the NCC group is the different from the CC group even in the concurrent observation time). We further assume that the treatment has no benefit compared with the up-to-date SoC, so the two hazard functions are the same. Depending on the randomization time, patients from the NCC group may experience different time in the nonconcurrent period before they witch to the concurrent time. As an illustration, the red line is the hazard function for patients randomized at time $t = 0$ where they switch to the concurrent period after 6 months. The red dashed line indicates the hazard function for patients randomized at time $t = 3$ where they enter the concurrent observation period after 3 months.

Table 3. Simulation results for the second simulation condition which assume the treatment group is the same as the CC group, but they have better performance compared with the NCC group.

Control group	Exponential		Weibull (decreasing hazard)		Weibull (increasing hazard)	
	RMST difference (bias) (MSE)	95%CI coverage (CI length)	RMST difference (bias) (MSE)	95%CI coverage (CI length)	RMST difference (bias) (MSE)	95%CI coverage (CI length)
CC + NCC	1.447 (−1.447) (2.291)	9.3% (0.884)	1.946 (−1.946) (4.106)	7.5% (1.135)	1.167 (−1.167) (1.486)	8.1% (0.705)
CC + NCC(COT)	0.451 (−0.451) (0.470)	86% (0.995)	0.708 (−0.708) (0.926)	80.3% (1.260)	0.370 (−0.370) (0.304)	85.6% (0.791)
CC	0.012 (−0.012) (0.306)	93.9% (1.072)	0.015 (−0.015) (0.493)	93.7% (1.364)	0.011 (−0.011) (0.190)	94.0% (0.852)
Flowchart	0.017 (−0.017) (0.310)	93.5% (1.071)	0.023 (−0.023) (0.501)	93.4% (1.362)	0.014 (−0.014) (0.193)	93.6% (0.851)

NOTE: The four rows represent four different methods to use the NCC data. The first method uses the entire NCC group data. The second method uses the NCC but concurrent observation time data. The third method uses only the CC group data. The last method uses the decision-making flowchart proposed in Section 2. We simulate survival data according to three different distributions, the exponential distribution, the Weibull distribution with increasing hazard and the Weibull distribution with decreasing hazard. For each simulated data, we calculate the estimated RMST difference compared with the treatment group, its bias (the truth is calculated using 100,000 times Monte Carlo method) and mean squared error. The table also provides the number of times that the estimated 95% CI covers the true value and the average length of the 95% CI.
NCC (COT): nonconcurrent control group in their concurrent observation time.

Table 4. The decision-making flowchart results for the second simulation condition.

	Exponential	Weibull (Decreasing hazard)	Weibull (Increasing hazard)
CC different with NCC	100%	100%	100%
CC different with the partially pooled control (CC+ NCC COT)	97%	97.4%	97.8%

NOTE: For each simulated distribution, the first row is the proportion of case that the CC group is significantly different from the NCC group (either the difference is statistically significant at level $\alpha = 0.05$ or clinically significant of 10% RMST change). the second row is the proportion of cases that the CC group is different from the partially pooled control.
NCC (COT): nonconcurrent control group in their concurrent observation time.

happens during a period of time (which may depend on country, region and/or clinic) such that using a single time point as left-truncation may be challenging. Another potential issue is that we use a fixed time window approach to define the concurrent observation period (i.e., the start time of the concurrent observation period is fixed as the time of the first randomized patient in the new treatment arm). However, the subsequent patients from CC group are randomized later than this start time and their SoC may continue to get updated if the accrual period of the CC group is relatively long. This can also lead to different SoC for the NCC patients in their concurrent observation time and the CC patients. Therefore, in practice, researchers should carefully compare the SoC for the two groups in the concurrent observation time before using the proposed decision-making flowchart to pool them together; (b) the Markov or conditional independence assumption that a patient's prior experience does not impact future survival probability. In our case we assume that the individuals' past care experience before the concurrent observation time do not affect their survival rate in the concurrent observation time given that they successfully enter the concurrent time. This is equivalent to view the hazard function to be dependent on a time-varying covariate in the nonconcurrent control group. While this assumption may or may not hold in some cases, this is actually the same assumption for the commonly applied approaches such as a time-varying covariate Cox model. (c) the patients randomized to NCC and CC are comparable conditional on covariates, as indicated by Lu et al. (2021). Here we did not include covariates in our illustration but the method can be easily extended to incorporate covariates. This assumption may be violated when the patient population changes rapidly. As an example during COVID-19 pandemic, patients are infected by different variants of COVID-19, and the vaccine status are likely to be different over time. As demonstrated in our second simulations, if the hazard functions are different due to population shift, borrowing information from the nonconcurrent control group may cause bias. Some literature recommended performing a sensitivity analysis to compare the results from borrowing the information of the nonconcurrent control data versus using the concurrent control data only (Angus et al. 2020b; Butler et al. 2021; Lee et al. 2021; Roig et al. 2021; Wang et al. 2023). If there is a difference either statistically significant or medical meaningful, researchers should be cautious on borrowing the information from the NCC data. In scenarios when the assumptions do not hold and a time trend is expected, we may consider a hybrid approach modeling the time trend during the concurrent time with left truncation.

Although in this article we propose to use the RMST in the decision-making steps and the final data analysis, other methods are also available to analyze the left-truncated and right-censored (LTRC) time-to-event data. The Cox proportional hazard model, which is widely used in analyzing the time-to-event data, can incorporate the left-truncation and censoring of the data (Cox 1972; Lin and Wei 1989; Reid and Cox 2018). Liu et al. (Liu et al. 2023) recently proposed to use the Cox PH model to analyze the pooled control group when borrowing the NCC concurrent observation time group data. The period analysis, often used in the context of HIV/AIDS research (Brenner, Gefeller, and Hakulinen 2004; Cox et al. 2007), can also

be applied to assess if there are changes in the control group over time. The period analysis aims to capture the survival trend change over time by splitting calendar time into different periods. Although this article does not cover all statistical approaches to handle LTRC, it employes the RMST method to illustrate the idea that methods for handling LTRC can be used to borrow the concurrent observation time of NCC.

Disclosure Statement

The authors report there are no competing interests to declare. Lu is employed by AstraZeneca; Roychoudhury, Huang, Meyer and Chu are employed by Pfizer. They own stocks of their companies.

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