Quantifying treatment differences in confirmatory trials with delayed effects

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Abstract

Dealing with non-proportional hazards is increasingly common nowadays when designing confirmatory clinical trials in oncology. Under these circumstances, the hazard ratio may not be the best statistical measurement of treatment effect, and nor is log-rank test since it will no longer be the most powerful statistical test. Possible alternatives include the restricted mean survival time (RMST), that does not rely on the proportional hazards assumption and is clinically interpretable, and the weighted log-rank test, which is proven to outperform the log-rank test in delayed effects settings. We conduct simulations to evaluate the performance and operating characteristics of the RMST-based inference and compared to the log-rank test and weighted log-rank test with parameter values ($\rho = 0, \gamma = 1$), as well as their linked hazard ratios. The weighted log-rank test is generally the most powerful test in a delayed effects setting, and RMST-based tests have, under certain conditions, better performance than the log-rank test when the truncation time is reasonably close to the tail of the observed curves. In terms of treatment effect quantification, the hazard ratio linked to the weighted log-rank test is able to capture the maximal treatment difference and provides a valuable summary of the treatment effect in delayed effect settings. Hence, we recommend the inclusion of the hazard ratio linked to the weighted log-rank test among the measurements of treatment effect in settings where there is suspicion of substantial departure from the proportional hazards assumption.

Keywords: delayed effects; non-proportional hazards; restricted mean survival time; weighted log-rank.

1 Introduction

Randomized controlled clinical trials are the gold standard in drug development to confirm both safety and efficacy of new drugs. When the primary endpoint is a time-to-event endpoint, the objective is to quantify the difference between the survival curves of the treatment arms. The most common time to event endpoints used for confirmatory phase III trials in oncology are: progression free survival (PFS) and overall survival (OS). PFS corresponds to the time from randomization until disease progression or death, whereas OS corresponds to the time from randomization until death.

In this article we focus on the application to the immuno-oncology (IO) space. IO agents have an effect on both the subject’s immune system and the tumor’s microenvironment. This way, the tumors may be eliminated from the host or the disease progression may be delayed. In contrast with chemotherapeutic agents, the effect of an IO agent is not directed to the tumor but to the subject’s
immune system, which causes that the effect is not observable immediately. This lag between the
activation of the immune cell is known in the literature as a delayed treatment effect. This delay
induces non proportional hazards and may translate to an overall underestimation of the PFS or
OS difference with respect to the control treatment arm (i.e., the hazard ratio (HR) may increase
towards 1, as the delay increases).

There exist in the literature multiple approaches to quantify treatment differences and test the
null hypothesis (HR=1) vs the alternative hypothesis (HR < 1) in confirmatory clinical trials.

The weighted log-rank test with the Fleming and Harrington class of weights [3] has gained, in
the recent years, considerable attention in the IO space as it allows to weight late differences between
survival curves over early differences by tuning its two parameters (ρ, γ). On this matter, [5] made
an extensive evaluation of the weighted log-rank test in confirmatory trials with delayed effects.
However, this comparison was made based only on power, and did not explore the quantification of
treatment effect.

[4] explored the differences between restricted mean survival time (RMST) and the hazard ratio
(HR) in a large number of scenarios that include proportional hazards and non proportional hazards.
The RMST is a robust and clinically interpretable measurement of the survival time distribution
that only depends on the selection of cutoff (truncation) time t∗ that needs to be pre-specified to
avoid selection bias (see [9]). Its clear advantage over the HR in a delayed effects setting is that it
does not rely on the proportional hazards assumption. Moreover, analogous to the hazard ratio as
a measurement of the relative risk of event hazard, a similar measurement for the RMST can be
obtained by simply doing the ratio of RMST between arms (control vs. experimental), with ratio
< 1 meaning survival benefit in the experimental arm. In the non proportional hazards setting in
which we are interested, the work from [4] concluded that the RSMT based tests are more efficient
that the log-rank test under certain censoring conditions (i.e., it achieves higher power). However,
the HR still gives a slightly better estimate of the maximal treatment differences, although as the
dropout rate increases the differences between the HR and the RMST ratio tend to disappear. This
article however does not include the performance of the weighted log-rank test (and its adjusted
HR), which is proven to be more powerful than the log-rank test in settings with delayed effects.
Mind that in [4] the HR used is a weighted average of the HR over time on the log scale and not
just the HR from the standard Cox model.

In this article extend the work of [4] and evaluate the differences in performance between RMST
based tests, and the weighted log-rank test with the parameter combination (ρ = 0, γ = 1), as well
as between the ratio between RMST of each treatment group, and the HR linked to the weighted
log-rank test and referred as “adjusted HR” (see section 2.2), in a setting with delayed effects. For
comparison purposes, we also include the HR in the comparison.

The rest of the manuscript is structured as follows. In section 2 we describe the weighted log-
rank test, the HR that is linked to the weighted log-rank test, and the RMST. In section 3 we
present an empirical evaluation between the log rank test, weighted log-rank test and RMST based
test in simulated scenarios with delayed effects. In section 4 we present an evaluation of a real trial
example. Last, in section 5 we discussion the major findings and conclusions of the article.

2 Method

Following the notation of [5], let T be a vector that contains the event times, t_i, i = 1, 2, ..., D, between
the patients’ enrollment date and the patients’ final event date, t_D, such that t_1 < t_2 < ··· < t_D. Let the number of events at time t_i be denoted as d_i, the total number of patients at
risk at that time be denoted as n_i, and the effect delay (in months) be denoted as ε. As previously
described if t < ε both survival curves go in parallel and once t ≥ ε, the survival curves will start
diverging. Hence, we assume the following density functions f_j(t), survival functions S_j(t) and
hazard functions $h_j(t)$ for the control group ($j = 1$) and for the experimental group ($j = 2$):

$$
f_1(t) = \lambda \exp(-\lambda t), \quad S_1(t) = \exp(-\lambda t) \quad \text{and} \quad h_1(t) = \lambda, \\
f_2(t) = \begin{cases} 
\lambda \exp(-\lambda t) \\
c\psi \lambda \exp(-\psi \lambda t)
\end{cases}, \quad S_2(t) = \begin{cases} 
\exp(-\lambda t) \\
c \exp(-\psi \lambda t)
\end{cases} \quad \text{and} \quad h_2(t) = \begin{cases} 
\lambda & \text{if } 0 \leq t < \epsilon \\
\psi \lambda & \text{if } t \geq \epsilon
\end{cases}, \quad (1)
$$

where $c = \exp\left[\epsilon \psi \lambda \left(\frac{1}{\psi - 1}\right)\right]$ so that $\int_0^\infty f_2(t) dt = 1$. This way, we assume a step function for the hazard ratio where from time 0 to $\epsilon$, the hazard ratio is equal to 1, and from time $\epsilon$ the hazard ratio is equal to $1/\psi$.

In this article we assume that the control group receives the standard of care and the experimental group receives a combination of the standard of care plus the IO agent which causes the delayed effect. Hence, any observed difference from time 0 until time $\epsilon$ is random and the conclusions we obtain are only applicable to studies where a similar assumption is made; otherwise, we cannot guarantee that from time 0 to time $\epsilon$, both groups have a common survival function.

2.1 Weighted log-rank test

The weighted log-rank test is defined as

$$Z_w = \frac{\sum_{i=1}^D w_{ti} (d_{1i} - E(d_{1i}))}{\sqrt{\sum_{i=1}^D w_{ti}^2 \text{Var}(d_{1i})}}, \quad (2)$$

where $E(d_{1i}) = n_{1i} \times \left(\frac{d_{1i}}{n_i}\right)$, $\text{Var}(d_{1i}) = \frac{n_{1i} n_{2i} d_{1i} (n_i - d_{1i})}{n_i^2 (n_i - 1)}$ and $Z_w \approx N(0, 1)$ under the null hypothesis (HR=1).

Fleming and Harrington (1981) [3] proposed the use of $w_i$ to weight early, middle and late differences through the $G^{\rho, \gamma}$ class of weighted log-rank tests, where the weight function at a time point $t_i$ is equal to

$$w_{ti} = \hat{S}(t_i)^\rho (1 - \hat{S}(t_i))^\gamma, \quad (3)$$

where $\hat{S}(t_i)$ corresponds to the Kaplan-Meier estimator.

Depending on the values of $\rho$ and $\gamma$, we will have different weight functions that will emphasize early differences ($\rho = 1, \gamma = 0$), middle differences ($\rho = 1, \gamma = 1$) or late differences ($\rho = 0, \gamma = 1$) in the hazard rates or the survival curves. The parameter combination ($\rho = 0, \gamma = 0$) attributes equal weights to all data values and hence does not emphasize any survival differences between treatment arms (i.e., the log-rank test).

Prior specification of $(\rho, \gamma)$ is always advisable for the trial integrity, although some authors (see e.g., [4]) note that the value of $(\rho, \gamma)$ can be modified at the interim analysis without type-I error rate inflation. The standard practice is to estimate, at the end of the trial, a hazard ratio across the entire study through the standard Cox model [2]. However, unless we use the parameter combination ($\rho = 0, \gamma = 0$), there will be a disconnect between the hazard ratio (i.e., the standard Cox model) and the weighted log-rank test. An adjusted HR is that incorporates the Fleming and Harrington class of weights in presented in section 2.2.

2.2 Hazard ratio linked to the weighted log-rank test

We follow the method proposed by [8] where, given the weight function $w_{ti}$ defined in equation (3), the effect adjustment factor $A_i$ is defined as
\[ A_{t_i} = \frac{w_{t_i}}{\max(w_{t_i})}. \] (4)

In (4), \( A_{t_i} \) is non-negative and has a maximal value 1. The hazard function in the Cox model proposed by [8] is defined as
\[ \lambda(t_i; X) = \lambda_0 e^{A_{t_i} \cdot \beta \cdot X} = \lambda_0 e^{\beta \cdot X_i}, \] (5)
where \( \lambda(t_i; X) \) has a constant coefficient and a time-varying covariate \( X_i = A_{t_i} \cdot X \) that represents the assignment weighted by the adjustment factor. The \( \hat{\beta} \) from the Cox models with time-varying coefficients are proven to be unbiased (see [1]).

Also, since \( A_{t_i} \leq 1 \), we can interpret \( \hat{\beta} \) as the estimated maximal effect. The time points where we observe the maximal treatment difference are weighted with \( A_{t_i} = 1 \) in the corresponding weighted log-rank test. Moreover, this weighted log-rank test (and consequently the score test from this model) is optimal and will have the highest power based on the Scenfeld’s proof [10].

The adjusted hazard ratio is therefore defined as
\[ HR_{t_i} = \frac{\lambda_0 e^{A_{t_i} \cdot \beta \cdot X}}{\lambda_0 e^{A_{t_i} \cdot \beta \cdot 0}} = e^{A_{t_i} \cdot \beta}, \] (6)
where \( e^{\beta} \) represents the maximal effect.

2.3 The restricted mean survival time

The RMST \( \mu \) of a random time to event variable \( T \) is a measure of the survival time distribution that does not require a proportional hazards assumption which is defined as the mean of the survival time \( Z = \min(T, t^*) \) truncated at time \( t^* > 0 \). It corresponds to the area under the survival curve \( S(t) = P(T > 0) \) defined from \( t = 0 \) to \( t = t^* \):
\[ \mu(t^*) = \int_0^{t^*} S(t)dt. \] (7)

The variance \( \sigma^2(t^*) \) of \( X \) is defined as
\[ \sigma^2(t^*) = 2 \int_0^{t^*}tS(t)dt - \left[ \int_0^{t^*} S(t)dt \right]^2. \] (8)

To estimate \( \mu \) in (7) we can use the Kaplan-Meier (KM) estimator of \( \hat{S}(t) \), hence
\[ \hat{\mu} = \int_0^{t^*} \hat{S}(t)dt. \] (9)
\( \hat{\mu}(t^*) \) approximately follows a normal distribution with variance
\[ V(\hat{\mu}(t^*)) = \sum_{i=1}^{D} \left[ \int_{t_i}^{t^*} \hat{S}(t)dt \right]^2 \frac{d_i}{Y_i(t_i - d_i)}, \] (10)
where \( d_i \) and \( Y_i \) are the number of events and number of subjects at risk at time \( t_i \) respectively.

The difference between treatment arms in terms of RMST is estimated as
\[ \int_0^{t^*} \left[ \hat{S}_E(t) - \hat{S}_C(t) \right] dt, \] (11)
where \( \hat{S}_E(t) \) and \( \hat{S}_C(t) \) are the estimated survival curves of the experimental and control arms respectively. The estimated variance term is defined as \( V(\hat{\mu}_E(t^*)) + V(\hat{\mu}_C(t^*)) \).

Since we have the RMST of both treatment arms, we can compute

\[
\frac{\int_0^{t^*} \hat{S}_E(t) \, dt}{\int_0^{t^*} \hat{S}_C(t) \, dt} \tag{12}
\]

Equation (12) is, just like the hazard ratio, a measurement of the relative risk of event hazard with ratio \(< 1\) indicating a survival improvement in the experimental arm. The variance of (12) is estimated using the delta method.

To have an objective evaluation, in this article \( t^* \) is linked to the data and is pre-specified as i) the minimum of the maximal observed event times (minimax event time) and ii) minimum of the maximal observed (event or censored) times (minimax observed time) of each treatment arm.

3 Simulated study

3.1 Setup

The simulation of the survival times \( T \) is conducted by randomly drawing sample from \( U(0, 1) \) and backtransforming using the inverse function \( S^{-1}_k(U) \). We assume that the dropout time variable \( D \) follows an exponential distribution with rate parameters \( \lambda_{DE} \) and \( \lambda_{DC} \) in the experimental arm and the control arm respectively. Again, following the notation of [4], let \( Y \) denote the time a subject is enrolled in the trial, and its distribution is the same in both treatment arms. We assume that \( T \) and \( D \) are independent and their distribution does not depend on \( Y \). The accrual and event times from different patients are also independent.

In total, we implement 2 scenarios with different delay times (\( \epsilon \)) that go from 0 (i.e., proportional hazards) up to 4 months delay. The median survival for the control arm is 6 months in both scenarios whereas the median survival for the experimental arm is 15 and 9 months respectively. Hence, the true hazard ratios (i.e., maximal treatment differences) will be 0.4 and 0.667 respectively as well. Sample size is calculated described above and using the Schoenfel’s formula (see [11]). Hence, the necessary number of events in each scenario is 52 and 258, and the total sample size 75 and 330 respectively.

The 2 scenarios with the different delays are implemented with different dropout rates that follow an exponential distribution with hazard rates of 1% and 3%. Data is generated using the nphsim R package [12] where we incorporate a 18 month enrollment (with ramp-up) period with administrative censoring at 25 months, randomization ratio 1:1, power of 90% and a one-sided level \( \alpha \) of 2.5%. We run \( M = 10,000 \) simulated trials where we calculate the empirical power defined as

\[
\text{Power} = \frac{1}{M} \sum_{i=1}^{M} I(z_{\text{test}}>z_{\alpha}). \tag{13}
\]

The evaluation of the RMST based test (minimax event time), the RMST based test (minimax observed time), the RMST ratio, the weighted log-rank test with the parameter combination \( \rho = 0, \gamma = 1 \), the log-rank test, the HR and the adjusted HR is implemented at the same time in the 2 presented scenarios.

3.2 Results

In Figures 1, 2, 3 and 4 we present the empirical comparison between RMST based tests and the weighted log-rank test with the parameters \( \rho = 0, \gamma = 1 \), and their respective treatment effect
difference estimates. Recall that the adjusted HR is the only method studied in this article that actually estimates the maximal treatment difference. The HR and the RMST provide a treatment differences across the entire study.

Figure 1 contains the results of scenario 1 where, under proportional hazards, the hazard ratio is equal 0.4 (i.e, the maximal treatment difference is hence 0.4). Overall, we can see that in terms of power, and as expected based on previous literature, the weighted log-rank test with the parameter combination \((\rho = 0, \gamma = 1)\) is the test with highest power as the delay increases. When the dropout rate is equal to 1% and the delay is equal to 0 (i.e., under proportional hazards), the log rank test has a power of 90% and is the most powerful test. The RMST based test (minimax observed time) performs slightly worse but outperforming both the RMST based test (minimax event time) and the weighted log-rank. However, when delay start to increase, weighted log-rank achieves the highest power, outperforming the log-rank test and the RMST based tests.

The weighted log-rank test remains the most powerful test also when the dropout rates increase to 3%. However, it is interesting to point out that, as the dropout rate and the delay increase, the RMST based test (minimax observe time) becomes slightly more powerful than the log-rank test.

Figure 3 contains the estimated treatment difference estimations in scenario 1. For both dropout rate, we observe that the HR provides a treatment difference across the entire study of 0.41 under proportional hazards, which increases up to 0.68 with a 4 month delay. Regarding the RMST ratios, the one using the minimax event time provides an estimate of the treatment difference of 0.62 under proportional hazards, increasing up to 0.83 with a 4 month delay. The RMST ratio that uses the minimax observed time provides an estimated treatment difference of 0.59 under proportional hazards that increases up to 0.78 with a 4 month delay. The adjusted HR provides a maximal treatment difference under proportional hazards of 0.42, which increases up to 0.54 with a 4 month delay.

Figure 2 contains the results of scenario 2 where, under proportional hazards, the hazard ratio is equal 0.667 (i.e, the maximal treatment difference is hence 0.667). Overall we can see that, just like in scenario 1, in terms of power the weighted log-rank test with the parameter combination \((\rho = 0, \gamma = 1)\) is the test with highest power as the delay increases. When the dropout rate is equal to 1% and the delay is equal to 0 (i.e., under proportional hazards), the log rank test has a power of 90% and is the most powerful test. The RMST based test (minimax observed time) performs slightly worse, but outperforming both the RMST based test (minimax event time) and the weighted log-rank test. However, when the delay starts to increase, the weighted log-rank achieves the highest power, outperforming the log-rank test and the RMST based tests.

The weighted log-rank test remains the most powerful test also when the dropout rates increase to 3%. However, it is interesting to point out that, as the dropout rate and the delay increase, in this scenario that has a smaller treatment difference between arms than the one from scenario 1 (i.e., the maximal treatment difference is scenario 1 is 0.4 and in scenario 2 is 0.667), both RMST based tests become more powerful than the log-rank test. This conclusion is in line with the conclusions made by [4].

Figure 4 contains the estimated treatment difference estimations in scenario 2. With a dropout rate of 1%, we observe that the HR provides a treatment difference across the entire study of 0.67 under proportional hazards, which increases up to 0.81 with a 4 month delay. Regarding the RMST ratios, the one using the minimax event time provides an estimate of the treatment difference of 0.75 under proportional hazards, increasing up to 0.86 with a 4 month delay. The RMST ratio that uses the minimax observed time provides an estimated treatment difference of 0.73 under proportional hazards that increases up to 0.85 with a 4 month delay. The adjusted HR provides a maximal treatment difference under proportional hazards of 0.67, which increases up to 0.73 with a 4 month delay. With a dropout rate of 3%, we observe that the HR provides a treatment difference across the entire study of 0.67 under proportional hazards, which increases up to 0.81 with a 4 month delay. Regarding the RMST ratios, the one using the minimax event time provides an estimate of
the treatment difference of 0.71 under proportional hazards, increasing up to 0.81 with a 4 month delay. The RMST ratio that uses the minimax observed time provides an estimated treatment difference of 0.71 under proportional hazards that increases up to 0.81 with a 4 month delay. The adjusted HR provides a maximal treatment difference under proportional hazards of 0.67, which increases up to 0.72 with a 4 month delay.

Overall, the simulations performed in this article provide the following conclusions:

- In line with [5], the weighted log-rank test with parameters \((\rho = 0, \gamma = 1)\) is the method that provides highest power in a setting with delayed effects.

- In line with the conclusions presented by [8], the adjusted HR that is linked to the weighted log-rank with parameters \((\rho = 0, \gamma = 1)\) test captures very well the maximal treatment difference between two treatment arms in the presence of delayed effects.

- In line with the conclusions from [4], the RMST based test using the minimax observed time outperforms in terms of power the log-rank test in the presence of delayed effects and increasing dropout rates. However, the HR yields a treatment difference across the entire study closer to the maximal treatment difference than the RMST ratios.

- Even though the HR and the RMST ratios do not try to estimate the maximal treatment difference, when used for this purpose as it is done in current practice, their estimation of the maximal treatment difference is, by far, not as good as the one provided by the adjusted HR.

Figure 1: Empirical power in scenario 1 for the log-rank test, the RMST bases test (minimax event time), RMST based test (minimax observe time) and the weighted log-rank test with the parameter combination \((\rho = 0, \gamma = 1)\) with dropout rates of 1% and 3%.
Figure 2: Treatment difference estimations in scenario 1 using the HR, the adjusted HR and RMST ratios with dropout rates of 1% and 3%.

Figure 3: Empirical power in scenario 2 for the log-rank test, the RMST bases test (minimax event time), RMST based test (minimax observe time) and the weighted log-rank test with the parameter combination ($\rho = 0, \gamma = 1$) with dropout rates of 1% and 3%.
4 Revisiting a real trial with delayed effects

In this section we exemplify the methodology reviewed so far with a real life trial setting [6]. In this trial, the HR was estimated to be 0.77 and we can observe that the effect does not kick in until month 15, as we can see in Figure 5. A total of 326 patients were 1:1 randomized to receive either inotuzumab ozogamicin (inotuzumab ozogamicin group) or standard intensive chemotherapy.

Assuming a 1% dropout rate, the HR is estimated to be 0.77, the HR linked to the weighted log-rank test takes a value of 0.67, and the RMST ratios take values of 0.80 and 0.87 using the minimax observed time and minimax event time respectively. In terms of estimated power, we obtained values of 0.59, 0.75, 0.65 and 0.40 using the log-rank test, the weighted log-rank test, and the RMST-based tests with minimax observed times and minimax event times respectively.

Assuming a 3% dropout rate, the HR is estimated to be 0.71, the HR linked to the weighted log-rank test takes a value of 0.56, and the RMST ratios take values of 0.64 and 0.66 using the minimax observed time and minimax event time respectively. In terms of estimated power, we obtained values of 0.78, 0.97, 0.94 and 0.90 using the log-rank test, the weighted log-rank test, and the RMST-based tests with minimax observed times and minimax event times respectively.

Again, we observe the same performance pattern as the one observe in the two simulated scenarios. The weighted log-rank test with parameter values ($\rho = 0, \gamma = 1$) achieves the highest power and the HR linked to this test is the one that better characterizes the treatment effect. We also observe that the dropout rate has an impact on power and treatment effect estimation. For a dropout rate of 1%, HR ratio outperforms RMST ratios, but when the dropout rates increases up to 3%, RMST ratios outperform the HR. The results comparing the HR with the RMST ratio are in line with the findings made by [4]. However, for both dropout rates, the HR linked to the weighted log-rank test is the one that performs best.

To do this comparison, we used stepwise exponential distributions with HR = 0.85 from month 0 to month 15, and with HR = 0.1 from month 15 until the end of the trial. These HR values result in survival curves very similar to the ones showed in Figure 5. Mind that it is out of the scope...
of this article to assess the results of this particular clinical trial. Its only purpose is to show the performance of the methodology used in this article in a real setting.

5 Discussion

Nowadays, it is quite common to find studies where the proportional hazard assumption does not hold (i.e., with the use of novel cancer therapies such as targeted therapies or immunotherapies). However, despite the fact that the HR lacks of interpretability under non proportional hazards, it is still the standard method to quantify treatment differences.

In this article we present a comparison between the log-rank test, the weighted log-rank test with parameters ($\rho = 0, \gamma = 1$) and RMST based tests, and their linked treatment difference estimates (i.e., the HR, the adjusted HR and RMST ratios), that are widely used in clinical trials with delayed effects. This article represents an extension of the work done by [4]. In the mentioned article, a comparison is done between log-rank and RMST-based tests (and their linked HR and RMST ratios). This comparison concludes that RMST ratios not only capture better the treatment differences but also can be interpreted, since they do not rely on the proportional hazards assumption. This comparison is done in a wide variety of scenarios, including non-proportional hazards. However, we believe that under non-proportional hazards, the weighted log-rank test and its linked HR are much more appropriate than both the HR and RMST ratios.

We implement all these methods (i.e., the log-rank test, the weighted log-rank test with parameter values ($\rho = 0, \gamma = 1$), RMST-based test, and their linked HRs and RMST ratios) in two scenarios...
with delayed effects and different dropout rates. From these simulations we conclude that under non-proportional hazards scenarios where late separation of survival curves is observed, the RMST-based test has better performance than the log-rank test in terms of power when the truncation time is reasonably close to the tail of the observed Kaplan Meier curves. However, the weighted log-rank test with parameters \((\rho = 0, \gamma = 1)\) outperforms both RMST-based tests and the log-rank test. In terms of treatment effect quantification, the HR linked to the weighted log-rank test is the measurement that performs best under non-proportional hazards.

The estimation of the treatment effect is also a key component of the analysis of a clinical trial. The RMST-based tests do not rely on any model assumptions and hence the interpretation is still straightforward. In contrast, the HR varies with time, and its value cannot be interpreted as the average HR across times. The RMST can capture the entire event-free distribution and hence is able to provide a clinically meaningful summary of the group differences in a randomized study. However, we believe that the HR linked to the weighted-log rank test also provides a good summary of the group differences by giving the maximal treatment difference observed along the entire trial, which can be easily interpreted under non-proportional hazards. Plus, it does not require to specify any truncation time unlike the RMST ratio. From our point of view this a clear advantage with respect to the RMST ration because if we design a study with the RMST as the primary analysis powered to detect a meaningful difference of 2 RMSTs, the selection of the truncation time cannot be based on the minimax event time or minimax observed time when data is not available. Instead, this truncation time should be a fixed timepoint. This time window has to be large enough and expected to capture most of the survival curves for the RMST to be used as an adequate global summary statistic. However, we believe that the maximal treatment difference is only useful in scenarios where there is a late separation between Kaplan-Meier curves. It would not make sense to provide this measurement for example in scenarios with crossing Kaplan Meier curves.

Therefore, under non-proportional hazard with late separation we agree with [4] when saying that the RMST curves as well as the related ratios are easy to interpret and are clinically meaningful to characterize the treatment effect over time and has a clear advantage over the HR and the log-rank test. However, we have shown that the weighted log-rank test with parameters \((\rho = 0, \gamma = 1)\) outperforms the RMST-based tests in terms of power and its linked HR provides a treatment difference summary that can be also very useful under the presence of delayed effects.

Software and data sharing

The R code used in the article is available at https://github.com/jjimenezm1989.

Disclaimer

The views and opinions expressed in this article are those of the author and do not necessarily reflect the official policy or position of Novartis Pharma A.G.

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