Design operating characteristics in a Non-Interventional Study framework

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Charlotte Wilhelm-Benartzi[1], Eileen Holmes[2], Anne Correges[1]

1. DSS for Evidence Generation-Data and Statistical Sciences Centre for RWE and EG. Daiichi Sankyo
2. Department of Statistics, Phastar

INTRODUCTION

- Non-interventional studies (NIS) are real-world studies important in generating evidence to gain deeper insights into how treatments work (1). Guidelines for NIS have been published by regulators including the FDA (2) and EMA (3); however further work is needed to establish good practice guidelines (1).
- For NIS, the study design characteristics such as sample size are usually specified by clinical operational considerations. Often, the rationale for that sample size is based on the precision of the primary endpoint estimate. However, a thorough understanding of the impact of other parameters, such as withdrawal rate on study design features will help to anticipate risk of unexpected observed values for these parameters.

OBJECTIVES

To support decisions on study design in NIS by exploring alternative operating characteristics using simulations. Looking at:

- How withdrawal rates affect the timing of the primary analysis.
- How withdrawal rates affect the probability of confidence interval overlap between treatments.

METHODS

Study Characteristics

- In this work, we consider a NIS in which patients can be treated either with the newly marketed drug (TRTn) or the conventional treatment (TRTc) at the discretion of the treating physician.
- The primary endpoint is a real-world time-to-event endpoint, rwTTE, such as rwTTNT1 (real world Time to Next Treatment).
- The primary objective is descriptive and aims to assess the median rwTTE for the patients treated with TRTn.

Simulations study design:

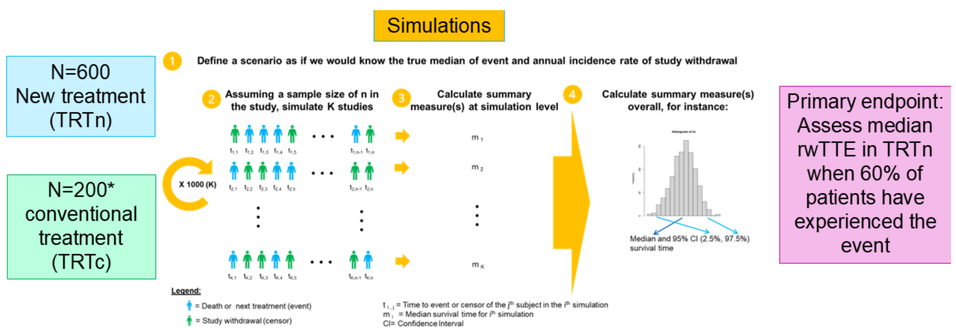
1000 simulations are run:

- As a proof of concept case, two cohorts of patients (TRTn and TRTc) are included in the scenario shown in Figure 1 which assumes 6 months median rwTTE for TRTn and 4.5 months for TRTc.
- Primary study completion is assumed to be when 60% of patients given the TRTn at study start meet the rwTTE primary endpoint criterion (i.e., 360 events). A uniformly distributed homogeneous Poisson point process is assumed for enrolment. Both the survival endpoint of interest and the withdrawal times are generated following an exponential distribution.
- Different median rwTTE (6-8 months) and annual withdrawal rates (0%, 10%, and 20%) are tested.
- Enrolment of 12 months per country is assumed with two waves of country group recruitment.

METHODS

The method of simulations is summarized in the following figure for our proof of concept case:

Figure 1: Simulation methods



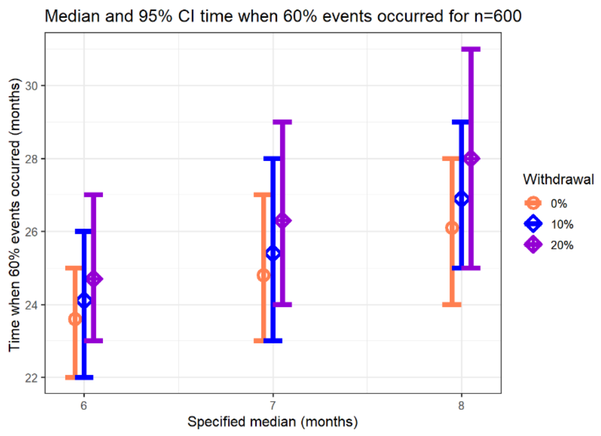
*optional to have an accompanying conventional therapy disease registry in a NIS but exemplified in this design context

RESULTS

Objective 1: How does the withdrawal rate influence the timing of the primary analysis?

- Using our proof of concept case described in the methods and assuming that 0% of the patients withdraw from the study, the mean time when 60% of primary events occur across the 1000 simulations is 23.6 months with a 95% CI of (22.1, 25.1).
- If the withdrawal rate is 10% (and 20% respectively), that median time increases to 24.1 months (24.7 months, respectively).
- The withdrawal rate has therefore an impact on the timing of primary analysis; this conclusion has also been also observed for other scenarios with true medians of 7 and 8 months (see Figure 2).
- Of note that in these simulations, no substantial impact of withdrawal rate on the precision of the estimate was observed.

Figure 2: Primary study completion scenarios



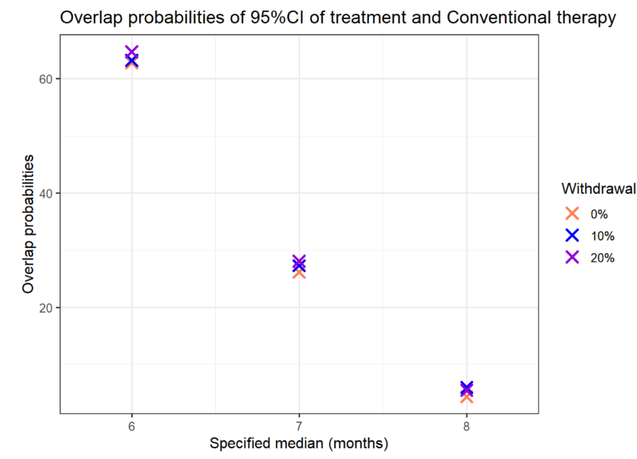
Objective 2: What is the potential overlap between results for the TRTn and TRTc arms?

- Although the primary objective of the study is focused on TRTn, the assessment of median rwTTE for patients treated with TRTc may be part of the exploratory objectives.
- Let's consider again our proof of concept case shown above assuming that 0% of the patients withdraw from the study: in that case the probability of having an overlap between the 95% CI associated to the observed median rwTTE of TRTn and TRTc is 62.8%.

RESULTS

- If the withdrawal rate is 10% (and 20% respectively), that probability increases slightly to 63.2% (64.7%, respectively).
- As the true rwTTE median for the treatment of interest increased, the overlap probabilities of 95% CI of the TRTn and TRTc decreased (see Figure 3).

Figure 3: Overlap probabilities of the 95% CI



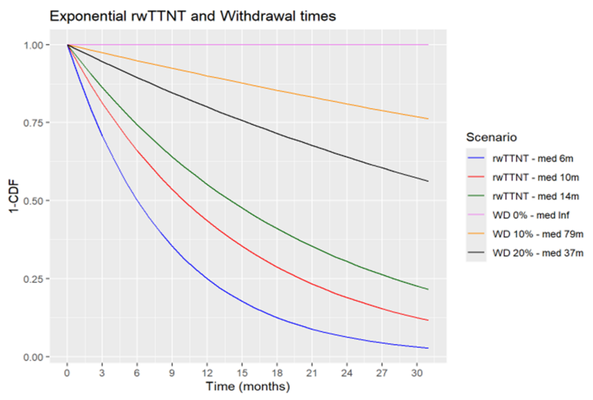
Other findings

- We examined the impact of looking at the data early and found that as the true rwTTE median for the TRTn and withdrawal rates increased, the number of events decreased. Early looks at data cuts can provide limited information due to low number of events.
- As expected, the precision was lower for rwTTE when recruitment was lower than the target sample size for the TRTn arm as exemplified by the wider 95% CIs of (4.7, 7.9) for 25% recruited, vs (5.3, 6.7) for 100% recruited for our base case.
- We looked at the probability of observing a shorter time to event and found that as the true rwTTE median increased, the probabilities of shorter median rwTTE decreased. This was not impacted by the withdrawal rate as the withdrawal was uninformative.

CONCLUSIONS

- Differing annual withdrawal rates had a small impact on our parameter estimates. We would anticipate a larger impact with longer rwTTE (as seen in Figure 4).
- This methodological approach can be extended to non-survival-based endpoints, and we believe that this framework can provide valuable information at the design stage, complementing the usual precision calculation approach, as well as allow for the closer monitoring of study parameters during study conduct.

Figure 4: Impact of withdrawal on rwTTE



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