Proceedings of the 2023 Winter Simulation Conference
C. G. Corlu, S. R. Hunter, H. Lam, B. S. Onggo, J. Shortle, and B. Biller, eds.

CONTINUOUS-TIME SURVIVAL MODEL STUDY DESIGNS FOR HEART RECOVERY APPLICATIONS

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ABSTRACT

Due to the aging global population, the science of heart recovery is an essential area for research to improve patient health, reduce time-to-discharge, and delay overall mortality. New medical device technology is needed to advance these goals. For the medical community to gain trust in and use these technologies in their hospital environments, optimal study design and proper execution of randomized controlled trials is necessary. Such RCTs will result in the collection of valid scientific evidence for establishing the new device's risk and benefit profile in targeted patient populations. Continuous time-to-event survival models are commonly used to determine the amount of data needed to demonstrate an improvement in these profiles over current standard-of-care therapies. This paper will compare simulated power functions and sample size requirements for a variety of survival methods in a two-sample RCT setting. Simulation scenarios will encompass various effect sizes, survival distribution forms, and time-to-event density functions.

1 INTRODUCTION

Careful consideration of *a priori* study design assumptions is important for optimizing the end-of-trial success of Class III (Post-Market Approval) protocols. These clinical trials commonly randomize subjects to either a new treatment arm or a reference group for comparative purposes. This effort is paramount for those Randomized Controlled Trials (RCTs) comparing mortality between treatment arms for subjects having various heart anomalies (e.g., cardiogenic shock, myocardial infarction). Conduct such trials is complicated by low enrollment rates per time period, expensive hospital care, and require many years for completion. The key metrics that frame the minimum bounds on such success are the likelihood of achieving the powered hypothesis set(s), detectable treatment effect, and number of subjects required for the desired subject population.

2 SOLUTION

An R-based tool was built to simulate end-of-trial planned and observed success for multiple statistical methods, endpoint assumptions, study design inputs, and subject characteristics in a cardiac pathophysiology RCT setting. Statistical methods comprise survival analysis techniques for the log-rank test (Kaplan Meier) and Cox regression (without and with baseline subject characteristics). Analysis is performed for linear survival endpoints with exponential, Weibull, and gamma time-to-event data distributions, and non-linear survival endpoints with Weibull mixture data distributions. Study design inputs consist of the treatment effect between comparison group, Type I and II errors, % LTFU (i.e., censoring), and subject sample size. Baseline subject characteristics associated with cardiac pathophysiology are cardiac production output (L/min), lactate (mmol/L), and age (years). Key outputs consist of simulated statistical power, minimum detectable treatment effect, and sample size requirements where all other study design options are held constant. The impact and delineation of these input options

and output expectations that minimize and maximize end-of-trial success is critical for study design finalization.

3 SOLUTION ARCHITECTURE

For each comparison group, time-to-event variables are modeled with binomial endpoints (i.e., mortality through 30 days: Yes/No) converted to hazard estimates $\theta = -\log_e(1 - p_i) /$ time. Random variates from the exponential-family probability density functions are simulated as $T_i \sim$ Exp(shape parameter = $\lambda = 1$, scale parameter = $\gamma = \theta$), $T_i \sim$ Wei($\lambda = 1$, $\gamma = 1/\theta$), and $T_i \sim \Gamma(\lambda = 1$, $\gamma = 1/\theta)$. Per each combination of study design options, these random values are generated in matrix form where column 1 is the subject id, column 2 is the treatment id (1 = new treatment; 0 = reference group), and columns 3 to *b+2* comprise the random values for each simulated data set. These matrices are then transposed by subject id and then analyzed in pseudo-parallel form with *by* feature within the *data.table* function.

Numerical analysis techniques are used to linearly interpolate results between study design input iterations. Multiple visualization tools are leveraged to assess the trustworthiness of simulation results. These outputs include histograms of observed versus target LTFU, contour plots of observed Test arm mortality error versus Reference group mortality error, and histograms of these errors individually.

4 BENEFITS

The solution's architecture was designed for analysis question flexibility while minimizing code run time. The solution generates a wide range of analysis outputs by setting multiple study design inputs through single code calls. The current solution leverages superiority hypothesis sets for an independent two-sample RCT approach. This solution can be extended to one-sample applications as well as comparator non-inferiority and equivalence objectives. This solution uses traditional survival analysis techniques for evaluating superiority hypothesis sets. The solution can be readily updated to reflect different statistical methods commensurate with study design objectives. Endpoint data are simulated for non-correlated linear and non-linear survival profiles with exponential family random variates through a 30-day window. The solution can be readily updated to reflect different correlation structures, functional forms, and distribution needs better suited to different design objectives.

This solution replaces traditional loops with a matrix-based vectorized approach for simulating desired study design options. For 2500 simulations with 21 condition iterations per each of 12 function calls, this architecture resulted in total run-time of 15.1 hours on a Windows machine (i7, 32Gb RAM) and 9.2 hours on a Macbook Pro (M1 Pro, 16 Gb RAM). This same output required ≈170 hours with a loop-based solution on the same Windows machine.

5 FUTURE DEVELOPMENT

Three areas were identified for advancing the utility of the current solution architecture for cardiac pathophysiology applications. First, such subject populations are known to discharge from the trial and then return to the trial with repeating cardiac symptoms, and in rarer cases, returning for care multiple times. For these data structures, survival analysis methods need to be extended for time-to-readmission subjects. Second, power function results are based on the non-parametric simulations of the desired random variates. Future efforts will improve the alignment between simulated and asymptotic power functions. Last, the current solution leverages visualization techniques to assess simulation quality. These techniques can lead to the improvement of simulation accuracy by information obtained from formal goodness-of-fit measures.