# Sample Size Formulas for Non-Inferiority Clinical Trials with Time-to-Event Data

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## ABSTACT

In many pharmaceutical studies, non-inferiority clinical trials are usually conducted because of the difficulty of finding a therapy that has more superior efficacy than a recognized effective one. When planning the non-inferiority clinical trials with a time-to-event endpoint, the calculation of sample size is one of the most fundamental steps. A proper sample size provides reasonable power to detect a clinically meaningful difference among groups. Currently exponential survival time assumption is usually made for planning a study. But, in cases that the hazard rate is not constant, the exponential assumption may be unsuitable. Thus, we introduce the sample size calculation formulas of another two distributions, Weibull and Gompertz distribution, in this paper to explore which distribution is more proper if hazard rate is not constant. The Weibull and Gompertz distribution, in which proportional hazard ratio holds, is more appropriate and flexible than exponential distribution for describing survival data because both include the shape parameter in addition to the scale parameter, which uniquely identifies the exponential distribution. Monte Carlo simulations are conducted to detect the applicability of three distribution sample formulas, in which various incidence rates, as well as increasing, constant, and decreasing hazard rates for Weibull and increasing hazard rates for Gompertz distribution, are taken into consideration. A two-tailed 95% confidence interval of the Cox proportional hazard model is used for inference. The simulation illustrates that exponential sample size formula may underestimate the sample size needed in cases where the hazard rate is increasing, and, moreover, may overestimate the sample size needed in cases where the hazard rate is decreasing. The calculated Gompertz sample size may be overlarge or too small depending on different parameter combinations. The empirical power from the Weibull distribution formula is around 0.8 in both scenarios. Therefore, we conclude that a Weibull distribution survival time assumption is suitable even if straightforward evidence supports the other two distributions of the survival time. An example is accordingly provided for illustration.

**Key Words:** Exponential distribution; Gompertz distribution; Survival analysis; Weibull distribution