Introduction to Clinical Trials

Lab 3: Sample size calculations

(i) Translational trials

Confidence Interval with Pre-Specified Halfwidth

To estimate the mean of a population, one typically uses the sample mean $\bar{X}$ as an estimator for the population parameter μ. The objective is to determine the sample size required to ensure that the estimation error of the mean is within $\mathrm{d} = 0.5 \cdot \sigma$ of the true mean, with a confidence level of 95%. This can be calculated using the formula for the sample size *n*:

$$n = \left(\frac{Z_{a/2} \cdot \sigma}{d}\right)^2$$

where $Z_{a/2}$ is the critical value from the Z-distribution corresponding to a 95% confidence level (approximately 1.96), and σ is the population standard deviation. The sample size must be adjusted based on estimated variability.

(ii) Testing for a Single Mean

To determine the sample size needed to test the hypothesis $H_0: \mu = 3$ against the alternative $H_1: \mu = 4$, assuming type I and II errors of 10% and a specified effect size of d = 2, one can utilize the "pwr" library in R. The Student's t-distribution should be used instead of the normal approximation due to potentially small sample sizes.

(iii) Phase II Sample Size Calculation

Revisiting the Phase II situation from the previous lab, we need to find the sample size required to test a null hypothesis with a type I error rate of 10% and a type II error rate of 20%. This can be accomplished using the exact binomial distribution via

"clinfun" library and applying arcsine transformation with the "pwr" library. The arcsine transformation is particularly useful for normalizing proportions and stabilizing variance.

(iv) Comparative Trials

In comparative trials testing the hypothesis $H_0: \mu_1 = \mu_2$ versus the two-sided alternative $H_1: \mu_1 \neq \mu_2$, it is assumed that both groups share a common standard deviation σ. It is essential to recreate Table 11.11 from Piantadosi (2005, pp. 280), which outlines various scenarios for sample sizes based on different effect sizes and power levels.

(v) Effects of Unequal Group Allocation

To illustrate the effects of unequal group allocation, one could design an example where participants are divided into two groups with different sizes. A graph should be constructed to display these findings, highlighting how unequal allocation impacts statistical power and variance estimates. Suggestions may include recommendations on optimal allocation ratios based on preliminary data.

(vi) Median Survival Time Analysis

Given that the median survival time for standard treatment is 15 months while an experimental treatment aims for 25 months:

Suppose that you are told that the median survival time of the standard treatment is 15 months whereas there is an experimental treatment that aims to increase the median survival time up to 25 months.

(a) Assuming that the hazard ratio remains constant over time, and under typical assumptions regarding death time distribution (exponential), one might estimate a hazard ratio of approximately:

$$HR = \frac{15}{25} = 0.6$$

(b) To design a survival study based on this hazard ratio, calculate the required sample size using nSurv from the "gsDesign" library, considering an accrual time of 55 months and an additional follow-up time of 10 months for a total study duration of 65 months. The significance level should be set at α=0.05 (two-sided).

(c) Repeat this calculation while accounting for a dropout rate of 0.009 in both groups.

(d) If considering an extension of follow-up to 100 months post-enrollment, reassess how this affects patient requirements due to increased follow-up time impacting overall power and study feasibility.

(e) With a fixed accrual rate of five patients per month and a maximum recruitment period of 35 months, compute how many patients need enrollment and determine necessary follow-up time after all patients have been enrolled.

(f) For a recruitment period involving five patients, illustrate through graphs how increasing follow-up from five months to 100 months affects sample size and accrual rate, providing observations on trends noted in these changes.