Introduction to Clinical Trials

Lab 2: Study designs

(i) Phase I Study

Consider a Phase I study conducted some time ago, aimed to determine the optimal dose of a cytotoxic drug. For the purposes of this lab, the optimal dose is defined as one that results in serious or life-threatening toxicity in no more than 30% of recipients. The study investigated ten different doses of the drug by randomly assigning each patient to receive exactly one dose. Import the data file "trialPh1.csv" into R.

(a) Examine the data and estimate the probability of toxicity as a function of the administered dose using a suitable generalized linear model (GLM).

(b) Based on your model, identify the optimal dose.

(c) Explain why you believe the approach used by the investigators cannot be applied in modern clinical trials. Provide reasons to support your opinion.

(ii) Alternative Approaches to Phase I Studies

Given that traditional Phase I studies are considered unethical, alternative approaches have been explored. One of the simplest methods is the classic three-up/three-down design. The algorithm for this method is as follows:

1. Initial Dose Assignment: Three patients are assigned to receive the initial dose.

   - If no dose-limiting toxicity (DLT) is observed in any of these patients, the trial proceeds by enrolling three additional patients at the next higher dose level

2. Monitoring for DLT:

   - If one patient experiences a DLT at any dose level, three additional patients are enrolled at the same dose level:

- If one or fewer out of six patients experience toxicity, three new patients are enrolled at the next higher dose level.
- If two or more out of six patients experience DLT, three new patients are enrolled at the previous dose level.

3. Escalation Criteria:

- If two or more out of the initial three patients experience DLT, three new patients are also enrolled at the previous dose level.

Let *b(k; n; p)* denote the binomial probability of observing *k* responses (toxicities) out of *n* subjects. The conditional probability of escalating past the *i*-th dose, given that this dose has been reached, can be expressed as follows:

$$P_i = b(0;3;p_i) + b(1;3;p_i) \times b(0;3;p_i),$$

where p_i is the true probability of observing a toxicity at the *i*-th dose. The unconditional probability of passing the *i*-th dose is given by:

$$Q_i = \prod_{k=1}^{i} b(0;3,p_k) + b(1;3,p_k) \times b(0;3,p_k).$$

The operating characteristic (OC) of the study, which represent the chance of stopping at or before a given dose, can be expressed as:

$$1 - Q_i$$

(a) Please explain how these formulas are derived.

(b) Create an R function to implement the three-up/three-down design. Your function should accept hypothetical probabilities of toxicity along with corresponding doses as input and return all relevant quantities of interest in a data frame. What is the probability of continuing past the second dose if the probability of toxicity is expected to be 20% for the first dose and 30% for the second dose?

(c) Using hypothetical probabilities of toxicity illustrated in Figure 10.2 of the textbook (Piantadosi, 2005, p. 235) as an example, calculate the OCs for both scenarios and plot the results.

(d) Assuming that an optimal dose is defined as one yielding a 30% toxicity rate, evaluate the performance of the three-up/three-down design in identifying this optimal dose.

(iii) Phase II Non-comparative Study

Consider a Phase II non-comparative study designed to assess one treatment's efficacy. We need to determine whether the response rate is at least 15%, which is currently considered standard. Based on prior evidence, we assume that the true response rate for the new treatment is 40%. Specify appropriate hypotheses (null and alternative), and construct an exact binomial test (i.e., specify the rejection region), assuming a sample size n = 16 and a type-I error rate $\alpha = 0.10$ (one-sided). What are the **exact** significance level and power of this test? Perform calculations in R and verify your results using the program `rsppow` (found in the course folder).

(iv) Sample Size Calculation for Simon's Two-stage Design

Suppose you need to calculate the sample size required for Simon's two-stage design in a Phase II clinical trial involving therapy mentioned in section (ii). You can use the function `ph2simon` from the `clinfun` library. Interpret the output in detail. What advantages does this two-stage design offer compared to single-stage designs?

(v) Example of a Cross-over Trial for Angina Pectoris

In this cross-over trial, researchers investigated pronethalol's effects on angina pectoris. A cross-over trial uses each participant as their own control, allowing each participant to receive more than one treatment and enabling comparisons within individuals across different treatments. The objective was to compare pronethalol

with placebo for treating angina pectoris. Patients received placebo for two periods of two weeks and pronethalol for two periods of two weeks, administered in random order (Pritchard et al., 1963). They completed diaries documenting their angina attacks.

(a) Import the data file into R and examine it. Assess whether a normal distribution would be reasonable for this data.

(b) Ignore matched cross-over design considerations and conduct a naive analysis (i.e., treat this study as a two-independent-sample clinical trial). Is there a significant treatment effect?

(c) Now consider study design by analyzing data as paired observations. What do you observe? Comment on your findings. What additional assumptions must you validate your results even with this analysis?