Chapter 720

Probit Analysis

Introduction

Probit and logit analysis may be used for comparative LD_{50} studies for testing the efficacy of drugs designed to prevent lethality. This program module presents calculates power and sample size using the methodology outlined in Kodell, Lensing, Landes, Kumar, and Hauer-Jensen (2010).

Technical Details

Consider the following situation: suppose two, equal-sized groups of animals are exposed to the same death-causing agent such as radiation. The test group of animals is exposed to a countermeasure drug, while the control group is not. The study's objective is to test whether the radiation LD_{50} of the treatment group is significantly greater than that of the control group.

Probit and logit analysis are often used to study the relative potency of a test treatment over a control treatment. The probit and logit transformations are

$$Y = F^{-1}(P) = \beta_0 + \beta_1 \log_{10}(D)$$

where *F*(x) is the cumulative normal distribution for the probit analysis and the cumulative logistic distribution for the logit analysis, β_0 is the intercept, β_1 is the slope, and *D* is the dose of the agent (radiation). Define $LD_{50}(T)$ as the lethal dose for 50% of the treated population and $LD_{50}(C)$ as the lethal dose for 50% of the control population. Finney (1978) provides methodology for estimating the relative potency (efficacy) using parallel, log-dose regression lines.

Let

$$\rho = \frac{LD_{50}(T)}{LD_{50}(C)}$$

and

$$\log_{10}(\rho) = \log_{10}\{LD_{50}(T)\} - \log_{10}\{LD_{50}(C)\}.$$

The null and alternative hypotheses are

$$H_0: \rho = 1$$

$$H_A: \rho > 1$$

or

$$H_0: \log_{10}(\rho) = 0$$

$$H_A: \log_{10}(\rho) > 0$$

Let

$$\theta = \log_{10}(\rho) = \frac{\beta_{0C} - \beta_{0T}}{\beta_1}$$

This can be estimated by

$$\hat{\theta} = \log_{10}(\hat{\rho}) = \frac{\hat{\beta}_{0C} - \hat{\beta}_{0T}}{\hat{\beta}_1}$$

The variance of $\hat{\theta}$ is estimated using

$$\hat{V}(\hat{\theta}) = \frac{s^2}{\hat{\beta}_1^2}\left[\sum_{T,C}\frac{1}{\sum_{i=1}^{g} w_i n_i} + \left\{\frac{(\bar{y}_T - \bar{y}_C)^2}{\hat{\beta}_1^2}\right\}\left\{\frac{1}{\sum_{T,C}\sum_{i=1}^{g} w_i n_i (x_i - \bar{x})^2}\right\}\right]$$

where n_i is the number of animals in the i[th] dose group and

$$w_i = \frac{\phi\left(\Phi^{-1}(P_i)\right)^2}{P_i(1-P_i)} \quad \text{for a probit analysis}$$

$$w_i = P_i(1-P_i) \quad \text{for a logit analysis.}$$

Note that $\phi(x)$ is the normal density function and $\Phi^{-1}(x)$ is the normal c.d.f.

The test statistic for testing H_0 versus H_A is

$$T = \frac{\hat{\theta}}{\sqrt{\hat{V}(\hat{\theta})}}$$

which has a *t* distribution with $f = 2g - 3$ degrees of freedom.

Using several simplifications and approximations, Kodell, et al. (2010) show that the sample size per dose group is given by

$$n = \frac{2\left(t_{f,1-\alpha} + t_{f,1-\beta}\right)^2}{\{\beta_1 \log(\rho)\}^2 \sum_{i=1}^{g} w_i}$$

The power is given by

$$t_{f,1-\beta} = \sqrt{n\left(\frac{\{\beta_1 \log(\rho)\}^2 \sum_{i=1}^{g} w_i}{2}\right)} - t_{f,1-\alpha}$$

The relative potency is given by

$$\rho = 10^A$$

where

$$A = \sqrt{\frac{2\left(t_{f,1-\alpha} + t_{f,1-\beta}\right)^2}{n\beta_1^2 \sum_{i=1}^{g} w_i}}.$$

Example 1 – Power for Several Sample Sizes

This example will calculate power for several sample sizes of a probit analysis study designed to compare the efficacy of a new drug as a countermeasure to radiation-induced lethality. Experimenters want to size the study so that they can detect a relative potency of 1.1. They also want to study values of 1.05 and 1.15. They would like to study the power at a significance level of 0.025 of samples of 5 to 55 subjects.

They want to use a five-dose study with doses of 11, 12, 13, 14, and 15 chosen so that lethalities of about 0.05, 0.275, 0.5, 0.725, and 0.95 are obtained.

Setup

If the procedure window is not already open, use the PASS Home window to open it. The parameters for this example are listed below and are stored in the **Example 1** settings file. To load these settings to the procedure window, click **Open Example Settings File** in the Help Center or File menu.

Design Tab	
Solve For	**Power**
Model	**Probit**
Alpha	**0.025**
n (Sample Size per Dose-Group)	**5 to 55 by 10**
Target Response Proportions	**0.05 0.275 0.5 0.725 0.95**
Input Dose Using	**Doses**
Doses (Control Group)	**11 12 13 14 15**
Rho (Relative Potency)	**1.05 1.1 1.15**

Plot Text Tab	
Decimal Places – Plot Probabilities	**3**

Output

Click the Calculate button to perform the calculations and generate the following output.

Numeric Reports

Numeric Results for a Design with 5 Doses

Solve For: Power

	Sample Size					
Power	Group n	Total N	Relative Potency Rho	Slope β1	Alpha	Beta
0.13140	5	50	1.05	23.07	0.025	0.86860
0.35831	15	150	1.05	23.07	0.025	0.64169
0.57645	25	250	1.05	23.07	0.025	0.42355
0.73782	35	350	1.05	23.07	0.025	0.26218
0.84126	45	450	1.05	23.07	0.025	0.15874
0.90340	55	550	1.05	23.07	0.025	0.09660
0.45238	5	50	1.10	23.07	0.025	0.54762
0.91337	15	150	1.10	23.07	0.025	0.08663
0.98342	25	250	1.10	23.07	0.025	0.01658
0.99541	35	350	1.10	23.07	0.025	0.00459
0.99834	45	450	1.10	23.07	0.025	0.00166
0.99927	55	550	1.10	23.07	0.025	0.00073
0.80614	5	50	1.15	23.07	0.025	0.19386
0.99367	15	150	1.15	23.07	0.025	0.00633
0.99920	25	250	1.15	23.07	0.025	0.00080
0.99980	35	350	1.15	23.07	0.025	0.00020
0.99993	45	450	1.15	23.07	0.025	0.00007
0.99997	55	550	1.15	23.07	0.025	0.00003

Power	The probability of rejecting a false null hypothesis when the alternative hypothesis is true.
n	The dose-group sample size.
N	The total of all dose-group sample sizes.
Rho	The Relative Potency. Rho = (50% Lethal Dose of Treatment) / (50% Lethal Dose of Control).
β1	The slope of regressing the probits (or logits) on the log10 doses.
Alpha	The probability of rejecting a true null hypothesis.
Beta	The probability of failing to reject the null hypothesis when the alternative hypothesis is true.

Summary Statements

A probit analysis study design with 5 doses considered will be used to test whether the treatment potency (to reduce lethality) is greater than the control potency (H0: Rho ≤ 1 versus Ha: Rho > 1, Rho = LD50(Trt) / LD50(Cntrl), where LD50 is the lethal dose for 50% of the population). The comparison will be made using a one-sided t-test, as described in Finney (1978) and Kodell et al. (2010), with a Type I error rate (α) of 0.025. The 5 control doses and corresponding target response proportions (lethalities) for each dose are described in the table. The slope of regressing the probits on the log (base 10) doses is 23.07. To detect a relative potency (treatment to control) of 1.05, with a sample size of 5 subjects from each of the 10 dose groups (5 treatment groups and 5 control groups) for a total of 50 subjects, the power is 0.1314.

Lethality Report

Group Number	Response Proportion Lethality	Weight w	Dose
1	0.050	0.22394	11
2	0.275	0.55843	12
3	0.500	0.63662	13
4	0.725	0.55843	14
5	0.950	0.22394	15
Total		2.20135	

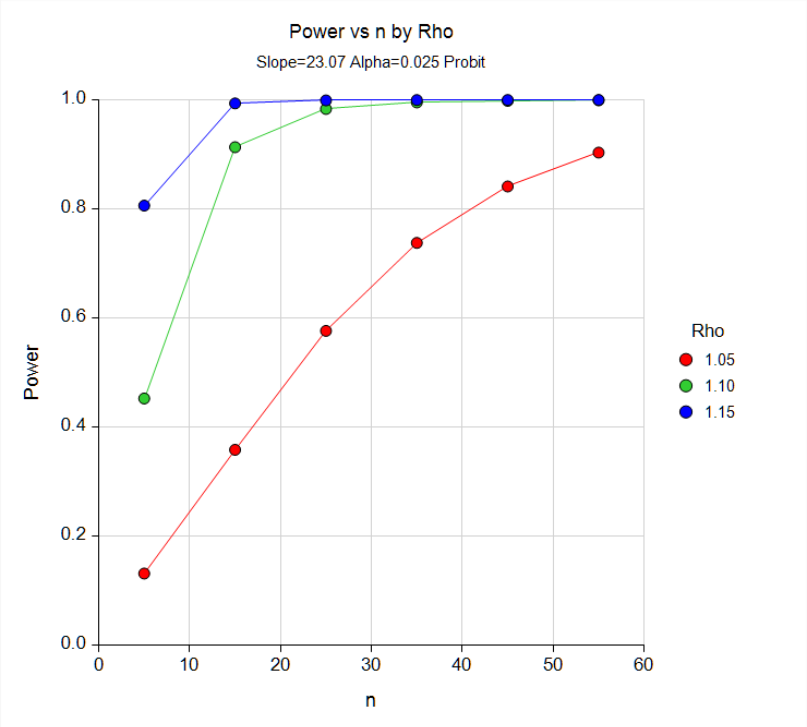
References

Kodel, R.L., Lensing, S.Y., Landes, R.D., Kumar, K.S., and Hauer-Jensen, M. March, 2010. 'Determination of Sample Sizes for Demonstrating Efficacy of Radiation Countermeasures.' Biometrics 66, 239-248.
Finney, D.J. Statistical Method in Biological Assay, 3rd Edition. Macmillan. New York.

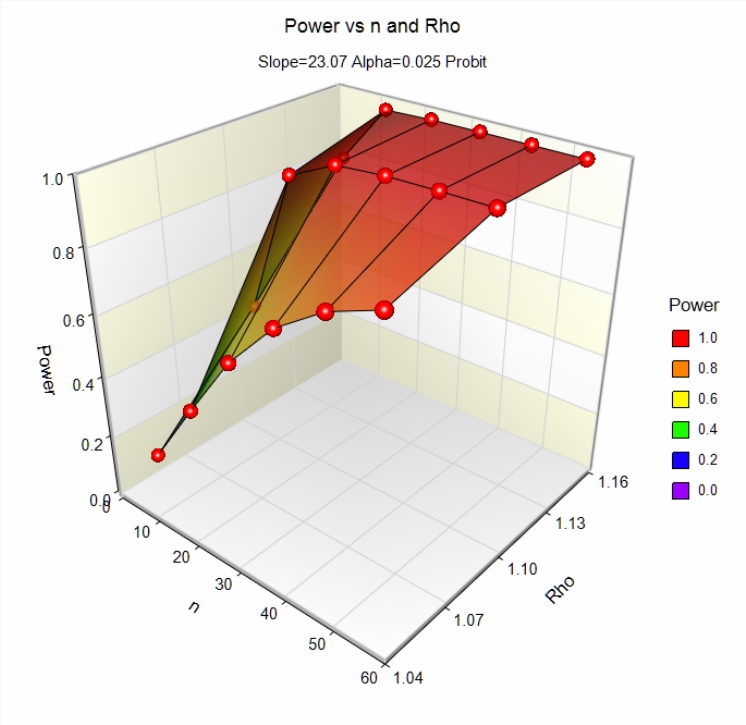
The first report shows the power for each of the scenarios. The lethality report gives the lethalities, weights, and doses for each group

Plots Section

Plots



Probit Analysis



Example 2 – Validation using Kodell et al. (2010)

We will validate this procedure using the results of Kodell et al. (2010). On page 243, in Table 2 of their article, Kodell et al. give the following example. For a five-dose example with target lethalities of 0.05, 0.275, 0.5, 0.725, 0.95, a slope of 23.25, rho of 1.1, power of 0.9, and alpha of 0.05, they obtain an *n* of 11.

Setup

If the procedure window is not already open, use the PASS Home window to open it. The parameters for this example are listed below and are stored in the **Example 2** settings file. To load these settings to the procedure window, click **Open Example Settings File** in the Help Center or File menu.

Design Tab	
Solve For	**Sample Size**
Model	**Probit**
Power	**0.90**
Alpha	**0.05**
Target Response Proportions	**0.05 0.275 0.5 0.725 0.95**
Input Dose Using	**Slopes**
Slopes	**23.25**
Rho (Relative Potency)	**1.1**

Output

Click the Calculate button to perform the calculations and generate the following output.

Numeric Results for a Design with 5 Doses

Solve For: Sample Size

	Sample Size					
Power	Group n	Total N	Relative Potency Rho	Slope β1	Alpha	Beta
0.90538	11	110	1.1	23.25	0.05	0.09462

Note that **PASS** has also calculated the required sample size at 11, or a total sample size of 110.