Chapter 131

Tests for One Poisson Rate with No Background Incidence (Post-Marketing Surveillance)

Introduction

This procedure computes power and sample size for a post-marketing surveillance, single-group, cohort design for a Poisson-distributed, count outcome variable. This procedure assumes that there is no background incidence of adverse reactions.

Post-Marketing Surveillance

Post-marketing surveillance, sometimes called a phase IV clinical trial, refers to the monitoring for effects and side-effects after a drug or regimen has successfully completed its phase III trial and has been cleared for general use. The field of *pharmacoepidemiology* studies issues that arise during phase IV. Such studies are usually observational in nature. There is no control over the delivery and monitoring of the regimen other than the routine oversight of the medical professional that has prescribed it. All effects, both intended and side, are monitored and evaluated.

Sometimes, a control group of those who have not received the regimen is added to the study. Occasionally, however, a control group is deemed unnecessary and only the *case* group is evaluated against known standards.

Technical Details

This section presents the formulas used to calculate sample size and power. The theory and formulas provided by Machin *et al.* (2018) are used.

Let the anticipated incidence rate of adverse reactions be R, the number of events of a particular adverse reaction be A, the number of subjects be N, and the probability that you will not find A or more events in the sample of N subjects be β. If R is small, the occurrence of an adverse reaction may be assumed to follow the Poisson distribution. If this is the case, the relationship among the above parameters is

$$\beta = \sum_{i=0}^{A-1} \frac{N^i R^i \exp(-NR)}{i!}$$

Using numerical search techniques, **PASS** can solve any one of these parameters in terms of the others. Note that this procedure does not explicitly set the probability of a type-1 error, alpha. Instead, it sets a value for A.

Example 1 – Finding the Power

Suppose 1 in 10,000 people receiving a certain drug are expected to have an irregular heartbeat. A researcher decides that if the irregular heartbeat occurs in three or more patients, the drug will have to be withdrawn.

In order to do this, sample sizes between 5,000 and 50,000 will be considered.

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**
N (Sample Size)..... **5000 to 50000 by 5000**
R (Incidence Rate)..... **0.0001**
A (Number of Events to Reject H0)..... **3**

Output

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

Numeric Reports

Numeric Results

Solve For: Power

Power	Sample Size N	Incidence Rate R	Reject H0 if Number of Events ≥ A	Beta
0.0144	5000	0.0001	3	0.9856
0.0803	10000	0.0001	3	0.9197
0.1912	15000	0.0001	3	0.8088
0.3233	20000	0.0001	3	0.6767
0.4562	25000	0.0001	3	0.5438
0.5768	30000	0.0001	3	0.4232
0.6792	35000	0.0001	3	0.3208
0.7619	40000	0.0001	3	0.2381
0.8264	45000	0.0001	3	0.1736
0.8753	50000	0.0001	3	0.1247

Power Equal to 1 - Beta.
N The total sample size. This is the number of patients monitored.
R The incidence rate of adverse reactions.
A The rejection number of adverse reactions. Reject H0 if number of events is greater than or equal to A.
Beta The probability that A reactions will not be found in the N patients.

Summary Statements

In a study with no background incidence of a specific adverse reaction, a single-group, post-marketing surveillance, cohort design will be used to determine whether there will be 3 or more adverse reactions. For an anticipated incidence rate of 0.0001 with a sample size of 5000 subjects, the power to detect 3 or more adverse reactions is 0.0144.

Dropout-Inflated Sample Size

Dropout Rate	Sample Size N	Dropout-Inflated Enrollment Sample Size N'	Expected Number of Dropouts D
20%	5000	6250	1250
20%	10000	12500	2500
20%	15000	18750	3750
20%	20000	25000	5000
20%	25000	31250	6250
20%	30000	37500	7500
20%	35000	43750	8750
20%	40000	50000	10000
20%	45000	56250	11250
20%	50000	62500	12500

Dropout Rate	The percentage of subjects (or items) that are expected to be lost at random during the course of the study and for whom no response data will be collected (i.e., will be treated as "missing"). Abbreviated as DR.
N	The evaluable sample size at which power is computed (as entered by the user). If N subjects are evaluated out of the N' subjects that are enrolled in the study, the design will achieve the stated power.
N'	The total number of subjects that should be enrolled in the study in order to obtain N evaluable subjects, based on the assumed dropout rate. N' is calculated by inflating N using the formula N' = N / (1 - DR), with N' always rounded up. (See Julious, S.A. (2010) pages 52-53, or Chow, S.C., Shao, J., Wang, H., and Lokhnygina, Y. (2018) pages 32-33.)
D	The expected number of dropouts. D = N' - N.

Dropout Summary Statements

Anticipating a 20% dropout rate, 6250 subjects should be enrolled to obtain a final sample size of 5000 subjects.

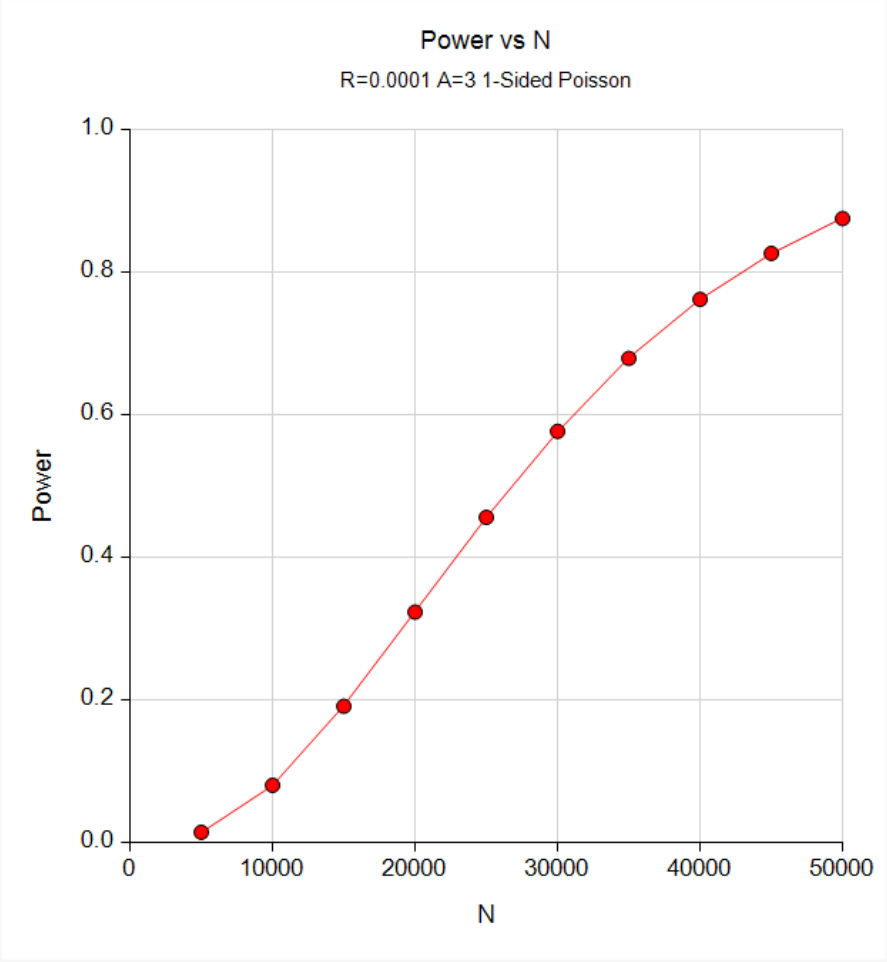
References

Machin, D., Campbell, M., Tan, S.B., and Tan, S.H. 2018. Sample Sizes for Clinical, Laboratory and Epidemiology Studies, 4th Edition. Wiley-Blackwell. Chichester, UK.

This report shows the calculated sample size for each of the scenarios.

Plots Section

Plots



This plot shows the power versus the sample size for A = 3.

Example 2 – Validation using Machin et al. (2018)

Machin *et al.* (2018) page 90 gives an example of a cohort design with no background incidence in which power is 99%, incidence is 0.0001, and *A* is 3. The computed sample size is 84,060.

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**
Power..... **0.99**
R (Incidence Rate)..... **0.0001**
A (Number of Events to Reject H0)..... **3**

Output

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

Numeric Results

Solve For: Sample Size

Power	Sample Size N	Incidence Rate R	Reject H0 if Number of Events ≥ A	Beta
0.99	84060	0.0001	3	0.01

PASS also calculates the required sample size to be 84,060. Thus, the procedure is validated.