

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 .

Procedure Options

This section describes the options that are specific to this procedure. These are located on the Design tab. For more information about the options of other tabs, go to the Procedure Window chapter.

Design Tab

The Design tab contains most of the parameters and options that you will be concerned with.

Solve For

Solve For

This option specifies the parameter to be solved for from the other parameters.

Power

Power

This option specifies one or more values for power. Power is the probability of rejecting a false null hypothesis and is equal to one minus Beta. Beta is the probability of a type-II error, which occurs when a false null hypothesis is not rejected.

Values must be between zero and one. Historically, the value of 0.80 (Beta = 0.20) was used for power. Now, 0.90 (Beta = 0.10) is also commonly used.

A single value may be entered here or a range of values such as *0.8 to 0.95 by 0.05* may be entered.

If your only interest is in determining the appropriate sample size for a confidence interval, set power or beta to 0.5.

Note that the interpretation of Power or Beta is a little different when the Design Type is 1.

Sample Size

N (Sample Size)

This is the sample size of the cohort being studied. In these types of studies, this number is usually quite large. The minimum value allowed is 2.

Effect Size

R (Incidence Rate)

This is the incidence rate of the adverse reaction that can be attributed to the treatment being monitored. This value must be greater than zero.

A (Number of Events to Reject H0)

This is the smallest number of events in the N subjects being monitored that will result in the null hypothesis of very low incident rate being rejected. Sometimes, only one drug-related adverse reaction (such as death) might be enough to make the drug unacceptable.

This value must be an integer greater than 0. The value of 1 is commonly used.

Options Tab

This tab sets a couple of options used in the iterative procedures.

Precision

Iterative Precision

When a search is made for the precision value, this is the cutoff value used to terminate the search. In most cases, a value of 0.0001 will be more than sufficient.

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

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the procedure window. You may then make the appropriate entries as listed below, or open **Example 1** by going to the **File** menu and choosing **Open Example Template**.

<u>Option</u>	<u>Value</u>
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

Annotated Output

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

Numeric Results

Numeric Results

Power	Size N	Incidence Rate R	Reject H0 if Number of Events \geq		Beta
			A		
0.0144	5000	0.00010	3		0.9856
0.0803	10000	0.00010	3		0.9197
0.1912	15000	0.00010	3		0.8088
0.3233	20000	0.00010	3		0.6767
0.4562	25000	0.00010	3		0.5438
0.5768	30000	0.00010	3		0.4232
0.6792	35000	0.00010	3		0.3208
0.7619	40000	0.00010	3		0.2381
0.8264	45000	0.00010	3		0.1736
0.8753	50000	0.00010	3		0.1247

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.

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Report Definitions

Power is $1 - \text{Beta}$.

N is the total sample size. This is the number of patients monitored.

R is the rejection number of adverse reactions.

A is the rejection number of adverse reactions. Reject H_0 if number of events is greater than or equal to A.

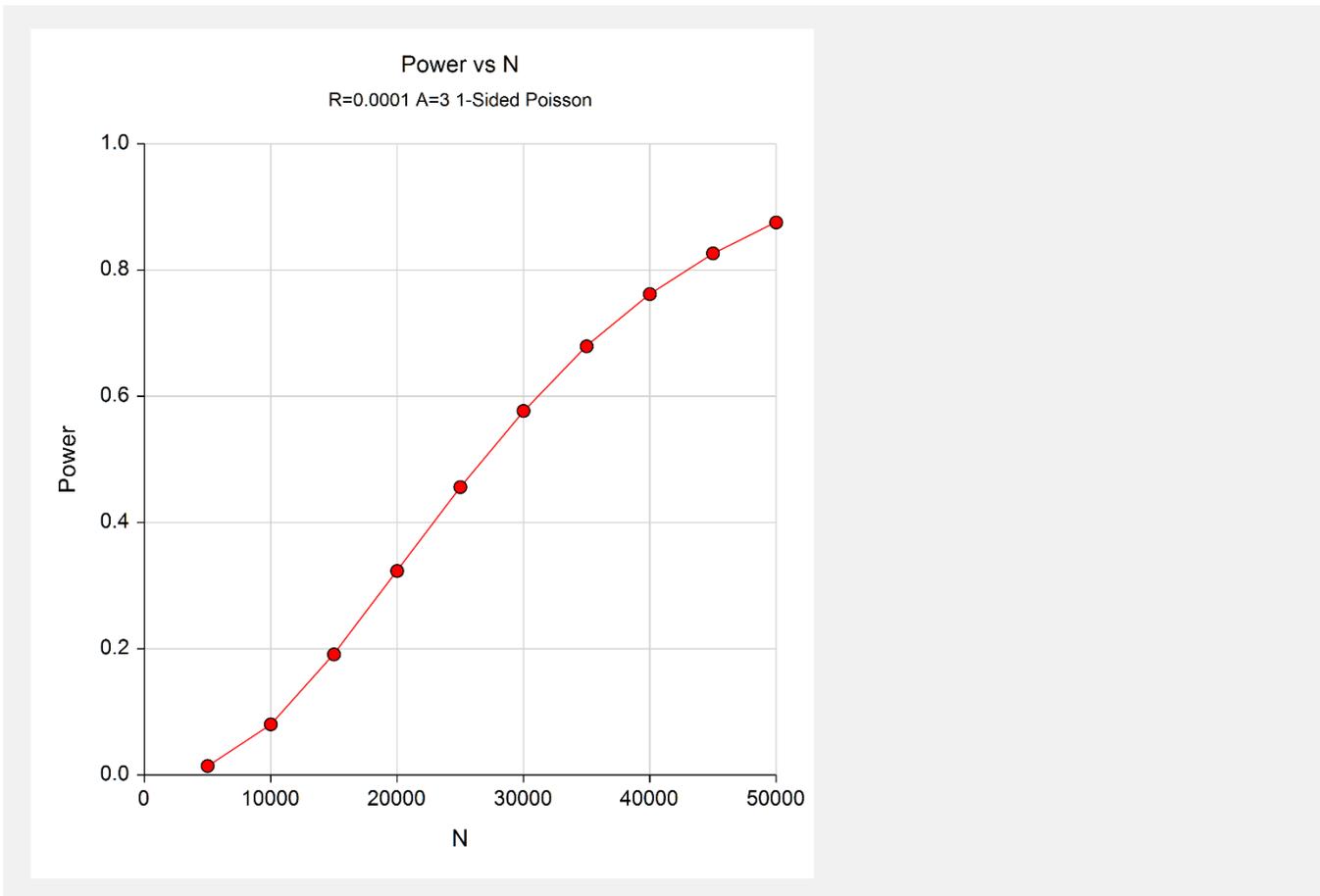
Beta is the probability that A reactions will not be found in the N patients.

Summary Statements

In a cohort study with no background incidence of a particular adverse reaction, the probability that 3 or more adverse reactions will not occur in a sample of 5000 subjects with an anticipated incidence rate of 0.00010 is 0.9856. The power of this study is 1%.

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

Plots Section



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 give 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

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the procedure window. You may then make the appropriate entries as listed below, or open

Example 2 by going to the **File** menu and choosing **Open Example Template**.

<u>Option</u>	<u>Value</u>
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				
	Size	Incidence	Reject H0	
	N	Rate	if Number	Beta
Power		R	of Events \geq	
			A	
0.9900	84060	0.00010	3	0.0100

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