Chapter 133

Tests for Two Poisson Rates with Background Incidence Estimated by the Control (Post-Marketing Surveillance)

Introduction

This procedure computes power and sample size for a post-marketing surveillance, two-group, cohort design for a Poisson-distributed, count outcome variable. This procedure assumes that the control group is not matched with the cases group. It requires the input of a background incidence rate 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.

This design adds an unmatched control group of those who have not received the regimen.

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. Note that the formulas used here were updated in the 4th edition of Machin's book. The results may not match older editions of PASS in those situations in which the two groups are not of the same size.

A control group is needed when the background incidence rate is not known. In post-marketing surveillance studies, the control group is usually made up of untreated individuals. Let the anticipated incidence rate of adverse reactions be *R0*, let the additional incidence rate caused by the drug be *D*, let the number of case subjects be *N1*,

and let the number of control subjects for each case be *M*. Thus, the number of control patients is *N1xM*. For a given significance level α and power $1-\beta$, the relationship between these parameters is

$$z_{1-\beta} = \frac{D\sqrt{MN1} - z_{1-\alpha}\sqrt{(1+M)R(1-R)}}{\sqrt{R0(1-R0) + M(R0+D)(1-R0-D)}}$$

where

$$R = \frac{MR0 + (R0 + D)}{1 + M}$$

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.

Test

Alternative Hypothesis

Specify whether the statistical test is two-sided or one-sided. The options are:

- **Two-Sided**
  The alternative hypothesis is that the two event rates are different (H1: rate 1 ≠ rate 2).
- **One-Sided**
  The alternative hypothesis is either that event rate 1 is less than the event rate 2 (H1: rate 1 < rate 2) or that event rate 1 is greater than the event rate 2 (H1: rate 1 > rate 2). The choice of less than or greater than is determined by the event rate values.

Appropriate Alpha

When you use a one-sided test, you should divide your alpha level by two to keep your results comparable with two-sided tests. For example, if you use 0.05 for a two-sided test, you would use 0.025 for a one-sided test.

T (Adverse Reactions Monitored)

Enter an integer for the number of different adverse reactions being simultaneously monitored by this study. The value of alpha used in the power and sample size calculations is replaced by alpha/T. For example, if there are 5 reactions being monitored, an alpha of 0.05 is automatically replaced with 0.05/5 = 0.01.

Often, a post-marketing surveillance study monitors for several different adverse reactions simultaneously. If these reactions can be assumed to have approximately equal incidence rates and act independently, a Bonferroni-correction can be made to alpha to correct for multiplicity. If the multiplicity is ignored many false positive results may occur.

Unfortunately, the Bonferroni Correction is known to be very conservative and it can cause much larger sample sizes. To avoid this, you must group several events together and determine an appropriate sample size for the group.

Bonferroni Correction

If *T* is the number of different events being monitored, alpha is replaced by alpha/T in power calculations.

Range

$T \geq 1$.

To ignore this correction, enter '1' here.

Power and Alpha

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.

Alpha

This option specifies one or more values for the probability of a type-I error. A type-I error occurs when a true null hypothesis is rejected.

Values between 0.001 and 0.100 are most common. The value of 0.05 is often a standard. This means that about one test in twenty will falsely reject the null hypothesis. Although 0.05 is a standard value, you should pick a value for alpha that represents the risk of a type-I error you are willing to take in your experimental situation.

Note that you can enter a range of values such as *0.01 0.05 0.10* or *0.01 to 0.05 by 0.01*.

Sample Size

N1 (Sample Size of Case Group)

This is the sample size of the case group. Cases are those subjects receiving the drug, regimen, or treatment. This number is often quite large.

Note that the number in the control group, N2, is equal to M x N1.

The value must be an integer greater than 1.

M (Controls Per Case)

This is the number of control subjects for each case subject.

Note that this value can be a decimal number.

Effect Size

R0 (Background Incidence Rate)

This is the background incidence rate of the adverse reaction. This is the rate that occurs in the population without the drug being monitored. It is the rate associated with the control group.

Since the sample size formula is based on the binomial distribution, both R0 and R0 + D must be less than one.

The values are constrained as follows: $0 < R0 < 1$ and $0 < D + R0 < 1$.

D (Additional Incidence Rate)

This is the additional incidence rate of the adverse reaction that can be attributed to the drug or regimen being studied.

R0 + D is the incidence rate used for the case group.

Since the sample size formula is actually based on the binomial distribution, both R0 and R0 + D must be less than one.

The values are constrained as follows: $-1 < D < 1$, $D \neq 0$, and $0 < D + R0 < 1$.

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 – Calculating the Sample Size

Suppose a new cancer treatment has successfully passed through a phase III trial and has reached the market. The investigators want to begin monitoring the drug for adverse reactions in the general population. Since the background incidence rate of these adverse reactions is not known certain, the investigators want to monitor a control group of the same size so that the adverse reaction incidence rates can be compared.

The investigators choose a one-sided alpha of 0.05, a power of 90%, an R0 of 0.003, and a D of 0.005. They decide to investigator various values of R0 from 0.001 to 0.005.

Determine the appropriate sample sizes.

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**.

Option	Value
Design Tab	
Solve For	**Sample Size**
Alternative Hypothesis	**One-Sided**
T (Adverse Reactions Monitored)	**1**
Power	**0.90**
Alpha	**0.05**
M (Controls Per Case)	**1**
R0 (Background Incidence Rate)	**0.001 to 0.005 by 0.001**
D (Additional Incidence Rate)	**0.005**

Annotated Output

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

Numeric Results

Numeric Results

Alternative Hypothesis: One-Sided

Power	Total Sample Size N	Controls Per Case M	Case Sample Size N1	Control Sample Size N2	Background Incidence Rate R0	Additional Incidence Rate of Cases D	Alpha
0.9000	4776	1.0	2388	2388	0.001	0.005	0.050
0.9000	6135	1.0	3067	3068	0.002	0.005	0.050
0.9000	7491	1.0	3745	3746	0.003	0.005	0.050
0.9000	8845	1.0	4422	4423	0.004	0.005	0.050
0.9000	10196	1.0	5098	5098	0.005	0.005	0.050

References

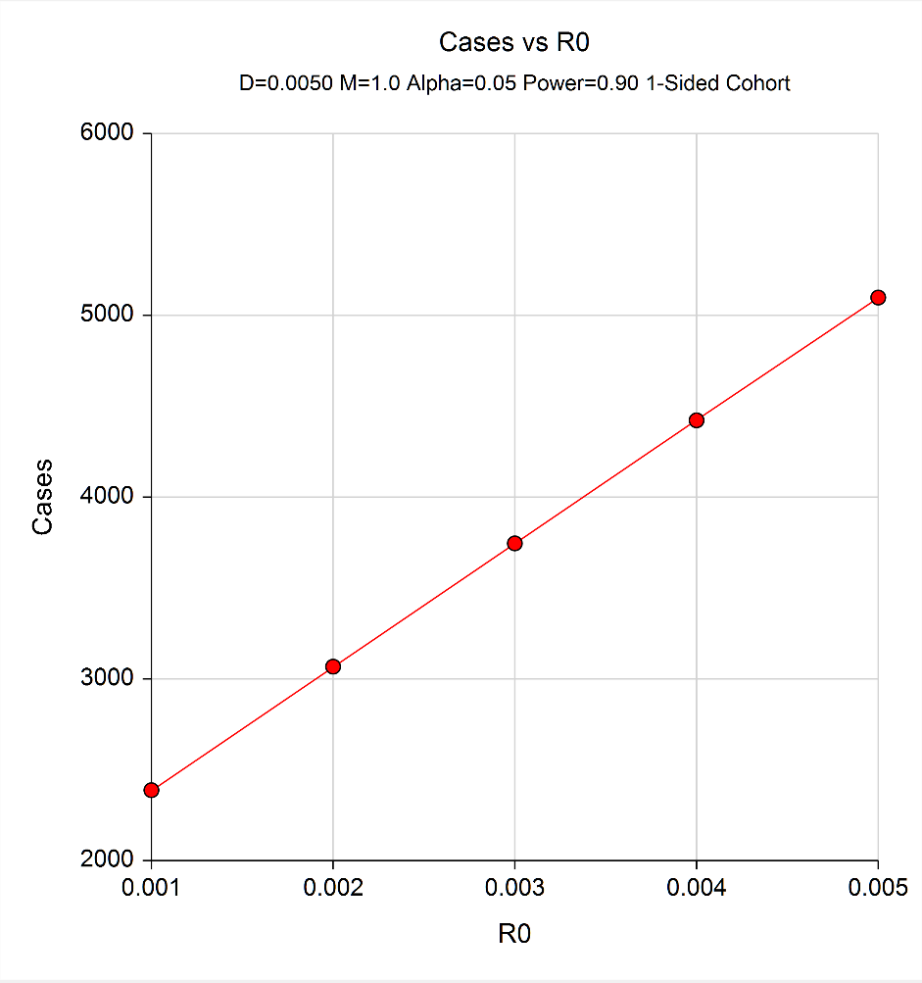
Machin, D., Campbell, M., Tan, S.B., and Tan, S.H. 2018. Sample Sizes for Clinical, Laboratory and Epidemiology Studies, 4th Edition. Wiley-Blackwell. Chichester, UK.

Report Definitions
Power is the probability of rejecting a false null hypothesis.
N is the total sample size.
M is the number of control subjects obtained for each case patient. No matching occurs.
N1 is the number of case (group 1) subjects.
N2 is the number of control (group 2) subjects.
R0 is the background incidence rate. This is the incidence rate of the control group.
D is the additional incidence rate above R0 added by the drug or regimen to the case group. Hence, the incidence rate of the case group is R0 + D.
Alpha is the probability of rejecting a true null hypothesis.

Summary Statements
In a cohort study with an unknown background incidence rate of a particular adverse reaction (which is estimated to be 0.001), a sample of 2388 cases and 2388 controls achieves 90% power to detect an additional incidence rate of 0.005 when alpha is 0.050.

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

Plots Section



This plot shows the number of cases required for each value of R0. It is assumed that a control group of equal size will also be enrolled in the study.

Example 2 – Adjusting for Multiple Adverse Reactions

This example will rerun Example 1, except that we will assume that there will be 5 adverse reactions monitored. In order to use the Bonferroni adjustment, we must be willing to assume that all 5 incidence rates are about the same and that the events are independent. We decide to make this assumption so we can see what happens to the sample sizes.

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**.

Option	Value
Design Tab	
Solve For	**Sample Size**
Alternative Hypothesis	**One-Sided**
T (Adverse Reactions Monitored)	**5**
Power	**0.90**
Alpha	**0.05**
M (Controls Per Case)	**1**
R0 (Background Incidence Rate)	**0.001 to 0.005 by 0.001**
D (Additional Incidence Rate)	**0.005**

Output

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

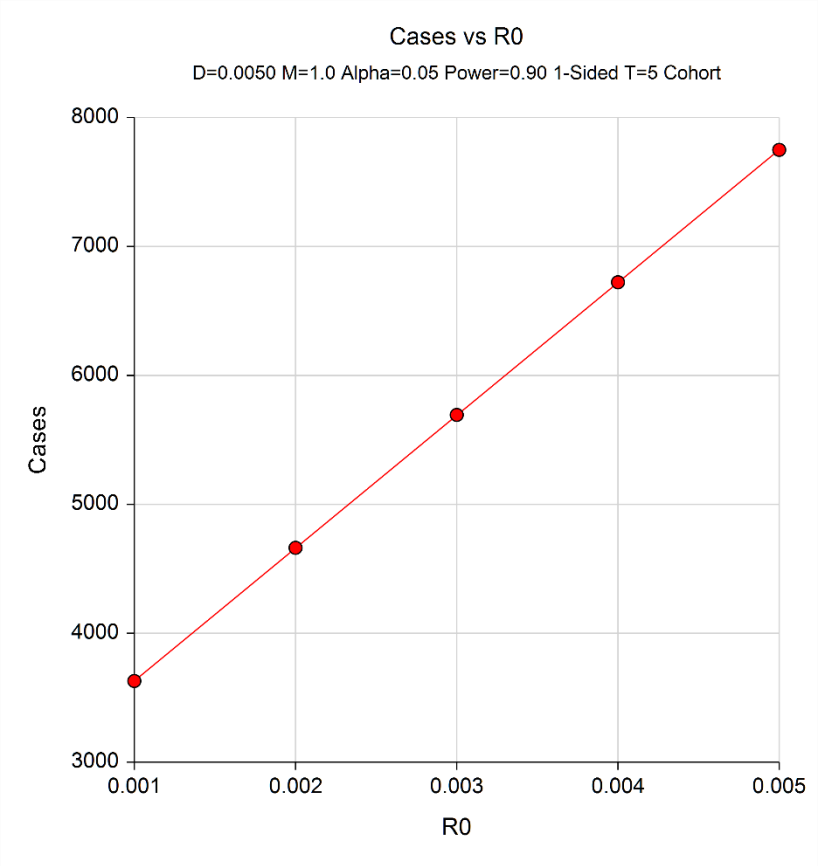
Numeric Results

Numeric Results
T (Adverse Reactions Monitored): 5
Alternative Hypothesis: One-Sided

Power	Total Sample Size N	Controls Per Case M	Case Sample Size N1	Control Sample Size N2	Background Incidence Rate R0	Additional Incidence Rate of Cases D	Alpha	Bonferroni-Corrected Alpha Alpha/T
0.9000	7260	1.0	3630	3630	0.001	0.005	0.050	0.010000
0.9000	9326	1.0	4663	4663	0.002	0.005	0.050	0.010000
0.9000	11388	1.0	5694	5694	0.003	0.005	0.050	0.010000
0.9000	13445	1.0	6722	6723	0.004	0.005	0.050	0.010000
0.9000	15499	1.0	7749	7750	0.005	0.005	0.050	0.010000

This report shows the calculated sample size for each of the scenarios after making the Bonferroni correction. Note that the sample size for the first scenario has increased from 4,776 in Example 1 to 7,260 now. This is an increase of only 52%.

Plots Section



This plot shows the number of cases required for each value of R0. It is assumed that a control group of equal size will also be enrolled in the study.

Example 3 – Validation using Machin et al. (2018)

Machin *et al.* (2018) page 92 gives an example of a two-group, cohort design with a background incidence of 0.01, a treatment incidence of 0.005, a power of 90%, and an M of 1. The required size of the case group is found to be 8456.

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

Option	Value
Design Tab	
Solve For	**Sample Size**
Alternative Hypothesis	**One-Sided**
T (Adverse Reactions Monitored)	**1**
Power	**0.90**
Alpha	**0.05**
M (Controls Per Case)	**1**
R0 (Background Incidence Rate)	**0.01**
D (Additional Incidence Rate)	**0.005**

Output

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

Numeric Results
Alternative Hypothesis: One-Sided

Power	Total Sample Size N	Controls Per Case M	Case Sample Size N1	Control Sample Size N2	Background Incidence Rate R0	Additional Incidence Rate of Cases D	Alpha
0.9000	16910	1.0	8455	8455	0.010	0.005	0.050

PASS calculates the case sample size (N1) to be 8455. This differs from the Machin's result of 8456 by 1. This difference occurs because the Machin example rounds the z-values to four decimal places.

Example 4 – Validation using Machin et al. (1997)

Machin *et al.* (1997) page 148 gives an example of a cohort design with unknown background incidence in which *N* is 8500, *R0* is 0.01, *D* is 0.005, and *A* is 1. The power is 90%.

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

Option	Value
Design Tab	
Solve For	**Power**
Alternative Hypothesis	**One-Sided**
T (Adverse Reactions Monitored)	**1**
Alpha	**0.05**
N1 (Sample Size of Case Group)	**8500**
M (Controls Per Case)	**1**
R0 (Background Incidence Rate)	**0.01**
D (Additional Incidence Rate)	**0.005**

Output

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

Numeric Results

Alternative Hypothesis: One-Sided

Power	Total Sample Size N	Controls Per Case M	Case Sample Size N1	Control Sample Size N2	Background Incidence Rate R0	Additional Incidence Rate of Cases D	Alpha
0.90136	17000	1.0	8500	8500	0.01000	0.00500	0.050

PASS calculates the same power value as did Machin *et al.* (1997).