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

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

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

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	**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**

Output

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

Numeric Reports

Numeric Results

Solve For: Sample Size
Alternative Hypothesis: One-Sided

	Sample Size				Incidence Rate		
Power	Case N1	Control N2	Total N	Controls per Case M	Background R0	Additional Cases D	Alpha
0.9	2388	2388	4776	1	0.001	0.005	0.05
0.9	3067	3068	6135	1	0.002	0.005	0.05
0.9	3745	3746	7491	1	0.003	0.005	0.05
0.9	4422	4423	8845	1	0.004	0.005	0.05
0.9	5098	5098	10196	1	0.005	0.005	0.05

Power The probability of rejecting a false null hypothesis when the alternative hypothesis is true.
N1 The number of case (group 1) subjects.
N2 The number of control (group 2) subjects.
N The total sample size.
M The number of control subjects obtained for each case patient. No matching occurs.
R0 The background incidence rate. This is the incidence rate of the control group.
D 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 The probability of rejecting a true null hypothesis.

Summary Statements

In a study involving a population with an unknown background incidence rate for a specific adverse reaction, a two-group, post-marketing surveillance, cohort design will be used to determine whether application of the new treatment increases the adverse reaction incidence rate. The presumed (or projected) background incidence rate is 0.001. A one-sided test will be used. To detect an additional incidence rate of 0.005 with 90% power and a Type I error rate (α) of 0.05, 2388 subjects will be needed in the case group and 2388 in the control group.

Dropout-Inflated Sample Size

	Sample Size			Dropout-Inflated Enrollment Sample Size			Expected Number of Dropouts		
Dropout Rate	**N1**	**N2**	**N**	**N1'**	**N2'**	**N'**	**D1**	**D2**	**D**
20%	2388	2388	4776	2985	2985	5970	597	597	1194
20%	3067	3068	6135	3834	3835	7669	767	767	1534
20%	3745	3746	7491	4682	4683	9365	937	937	1874
20%	4422	4423	8845	5528	5529	11057	1106	1106	2212
20%	5098	5098	10196	6373	6373	12746	1275	1275	2550

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.
N1, N2, and N	The evaluable sample sizes at which power is computed. If N1 and N2 subjects are evaluated out of the N1' and N2' subjects that are enrolled in the study, the design will achieve the stated power.
N1', N2', and N'	The number of subjects that should be enrolled in the study in order to obtain N1, N2, and N evaluable subjects, based on the assumed dropout rate. After solving for N1 and N2, N1' and N2' are calculated by inflating N1 and N2 using the formulas N1' = N1 / (1 - DR) and N2' = N2 / (1 - DR), with N1' and N2' 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.)
D1, D2, and D	The expected number of dropouts. D1 = N1' - N1, D2 = N2' - N2, and D = D1 + D2.

Dropout Summary Statements

Anticipating a 20% dropout rate, 2985 subjects should be enrolled in Group 1, and 2985 in Group 2, to obtain final group sample sizes of 2388 and 2388, respectively.

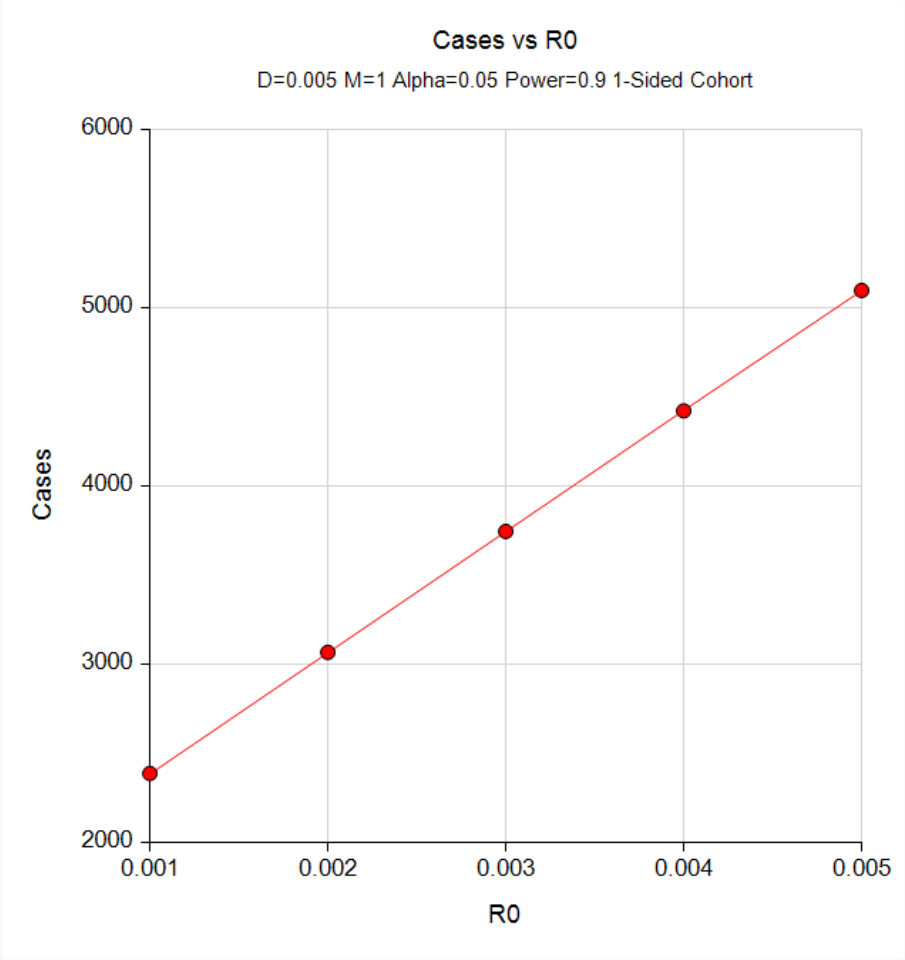
References

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 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

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**
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 Reports

Numeric Results

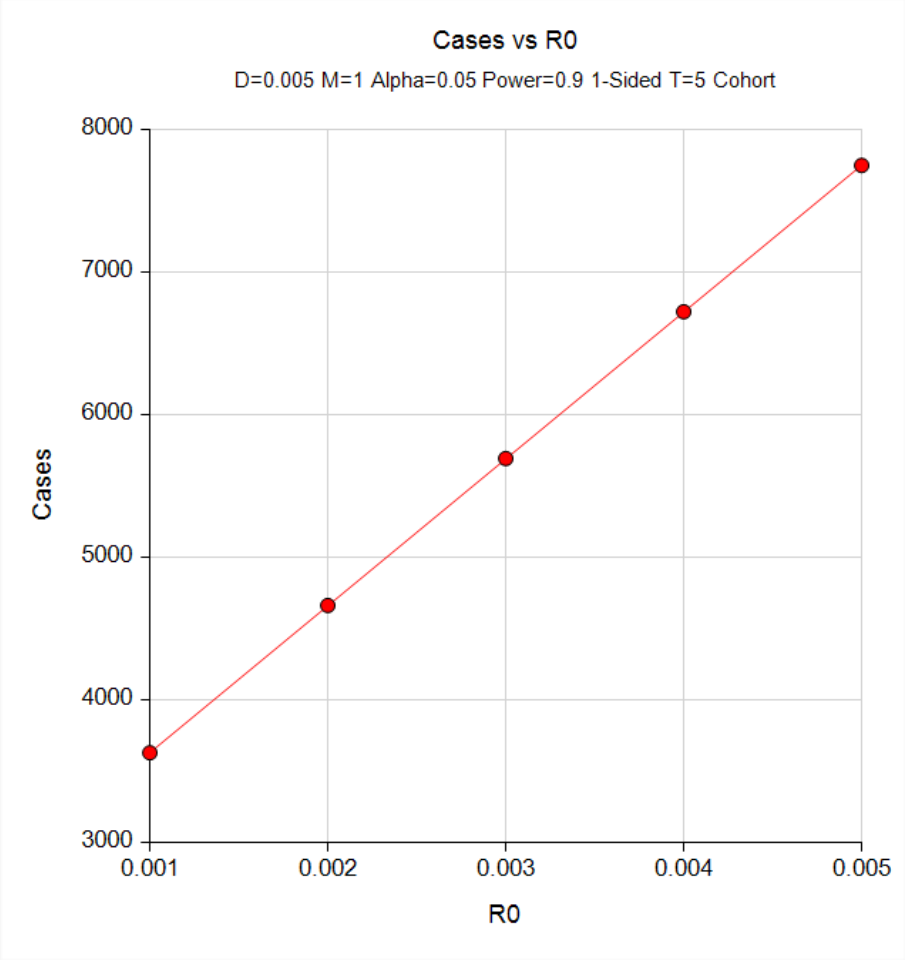
Solve For:	Sample Size
Alternative Hypothesis:	One-Sided
T (Adverse Reactions Monitored):	5

	Sample Size				Incidence Rate			
Power	Case N1	Control N2	Total N	Controls per Case M	Background R0	Additional Cases D	Alpha	Bonferroni-Corrected Alpha Alpha/T
0.9	3630	3630	7260	1	0.001	0.005	0.05	0.01
0.9	4663	4663	9326	1	0.002	0.005	0.05	0.01
0.9	5694	5694	11388	1	0.003	0.005	0.05	0.01
0.9	6722	6723	13445	1	0.004	0.005	0.05	0.01
0.9	7749	7750	15499	1	0.005	0.005	0.05	0.01

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

Plots



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

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 3** 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**
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

Solve For: Sample Size
Alternative Hypothesis: One-Sided

	Sample Size				Incidence Rate		
Power	Case N1	Control N2	Total N	Controls per Case M	Background R0	Additional Cases D	Alpha
0.9	8455	8455	16910	1	0.01	0.005	0.05

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

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 4** 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**
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

Solve For: Power
Alternative Hypothesis: One-Sided

	Sample Size				Incidence Rate		
Power	Case N1	Control N2	Total N	Controls per Case M	Background R0	Additional Cases D	Alpha
0.90136	8500	8500	17000	1	0.01	0.005	0.05

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