Chapter 135

Tests for Two Poisson Rates in a Matched Case-Control Design (Post-Marketing Surveillance)

Introduction

This procedure computes power and sample size for a post-marketing surveillance, two-group, matched case-control design. This procedure assumes that the control group is 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 includes a matched 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.

A case-control design involves identifying a group of patients that have experienced the reaction of interest and then obtaining matched control subjects that have not experienced the reaction. Every case subject has at least one matching control subject.

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 patients be *N1*, and let the number of control patients matched with each treated patient be *M*. For a given significance level α and power $1-\beta$, the relationship between these parameters is

$$z_{1-\beta} = \frac{|R0-\Omega|\sqrt{M(N1)} - z_{1-\alpha}\sqrt{(1+M)\Pi(1-\Pi)}}{\sqrt{R0(1-R0)} + M\Omega(1-\Omega)}$$

where $\Omega = \frac{R0+D}{1+D}$ and $\Pi = \left(\frac{R0}{1+M}\right)\left(M + \frac{\Omega}{R0}\right)$.

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 for certain, the investigators want to monitor a control group of the same size so that the adverse reaction incidence rates can be compared. They decide to use a matched case-control study.

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 investigate 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	2407	2407	4814	1	0.001	0.005	0.05
0.9	3099	3099	6198	1	0.002	0.005	0.05
0.9	3793	3793	7586	1	0.003	0.005	0.05
0.9	4488	4488	8976	1	0.004	0.005	0.05
0.9	5184	5184	10368	1	0.005	0.005	0.05

Power The probability of rejecting a false null hypothesis when the alternative hypothesis is true.
N The total sample size.
N1 The number of case (group 1) subjects.
N2 The number of control (group 2) subjects.
M The number of matching control subjects obtained for each case patient.
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

A matched case-control, post-marketing surveillance study 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 for the adverse reaction of interest 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, 2407 case subjects will be needed with 1 matching control subject per case subject, for a total of 4814 needed subjects.

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%	2407	2407	4814	3009	3009	6018	602	602	1204
20%	3099	3099	6198	3874	3874	7748	775	775	1550
20%	3793	3793	7586	4742	4742	9484	949	949	1898
20%	4488	4488	8976	5610	5610	11220	1122	1122	2244
20%	5184	5184	10368	6480	6480	12960	1296	1296	2592

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, 3009 subjects should be enrolled in Group 1, and 3009 in Group 2, to obtain final group sample sizes of 2407 and 2407, respectively.

References

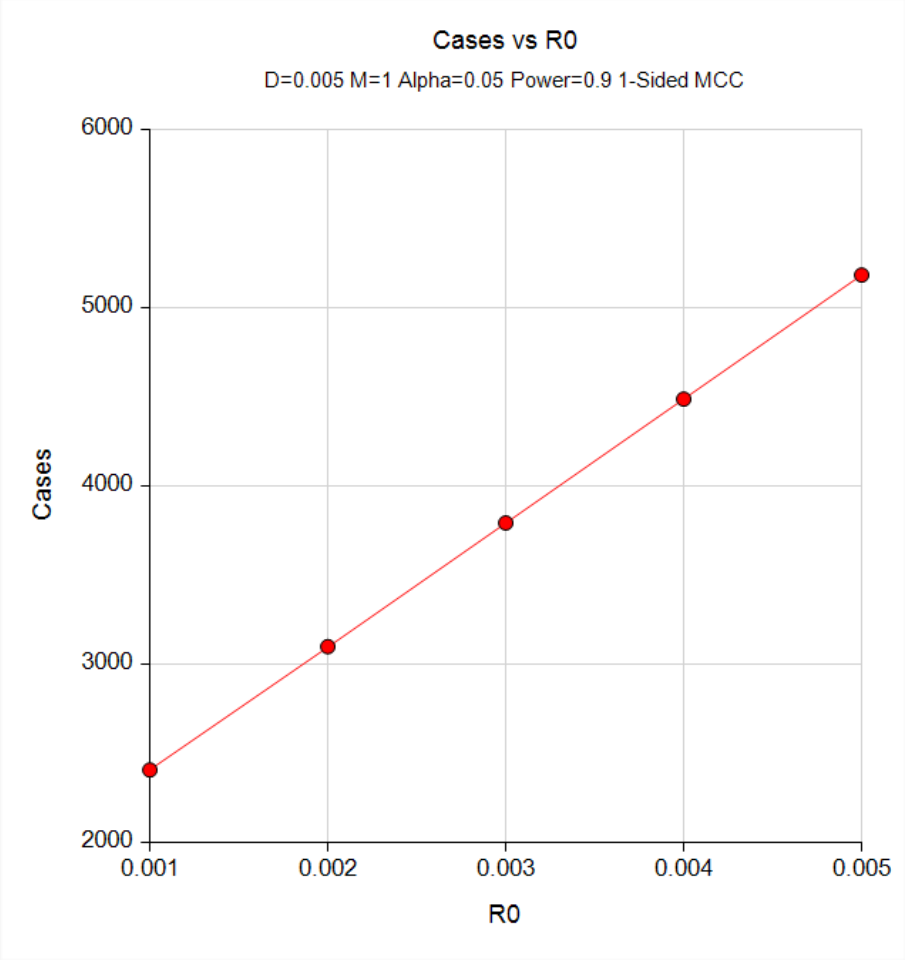
Machin, D., Campbell, M., Tan, S.B., and Tan, S.H. 2018. Sample Sizes for Clinical, Laboratory and Epidemiology Studies, 4th Edition. Wiley-Blackwell. Chichester, UK.

Strom, B.L, Kimmel, S.E., Hennessy, S. 2013. Textbook of Pharmacoepidemiology, 2nd 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 have to 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

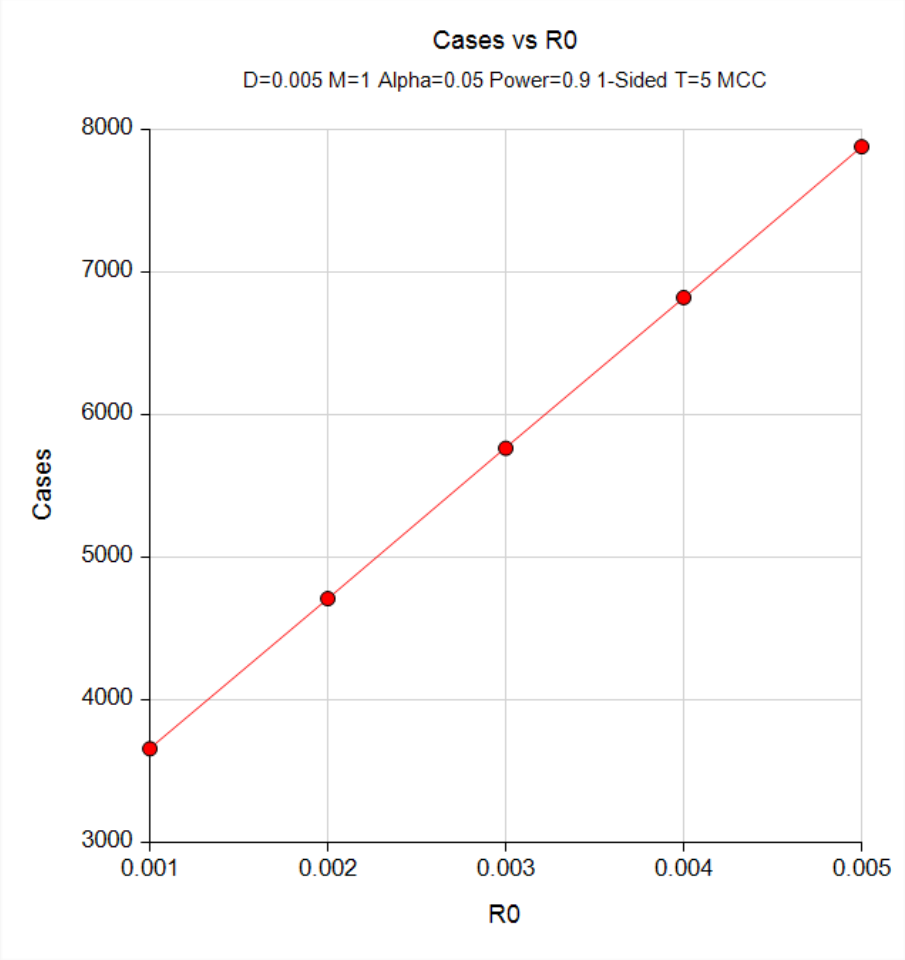
Solve For:	Sample Size
Alternative Hypothesis:	One-Sided
T (Adverse Reactions Monitored):	5

	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	3658	3658	7316	1	0.001	0.005	0.05	0.01
0.9	4711	4711	9422	1	0.002	0.005	0.05	0.01
0.9	5765	5765	11530	1	0.003	0.005	0.05	0.01
0.9	6822	6822	13644	1	0.004	0.005	0.05	0.01
0.9	7880	7880	15760	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 4814 in Example 1 to 7,316 now. This is an increase of 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) pages 92-93 gives an example of a two-group, matched case-control study with a background incidence of 0.05, a treatment incidence of 0.01, a power of 80%, and an M of 1. The required size of the case group is found to be 7236.

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	**0.8**
Alpha	**0.05**
M (Controls Per Case)	**1**
R0 (Background Incidence Rate)	**0.05**
D (Additional Incidence Rate)	**0.01**

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
0.8	7227	7227	14454	1	0.05	0.01	0.05

PASS calculates the case sample size to be 7227. This differs from the Machin's result of 7236 because the Machin example rounds the intermediate calculation values to only four decimal places.