Chapter 132

# Tests for One Poisson Rate with Known 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 a known background incidence rate.

## 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.

Often, 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 *R0*, let the additional incidence rate caused by the drug be *D*, and let the number of patients be *N*. For a given significance level $\alpha$ and power $1-\beta$, the relationship between these parameters is

$$z_{1-\beta} = \frac{D\sqrt{N} - z_{1-\alpha}\sqrt{R0}}{\sqrt{R0 + D}}$$

# 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 as a whole.

**Bonferroni Correction**

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

**Range**

T ≥ 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

### 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

### 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 or regimen being monitored.

This value must be greater than zero.

### 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.

#### Range

$D \neq 0$. $R0 + D > 0$.

## 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 3 in 10,000 people receiving a certain drug are expected to have an irregular heartbeat. Further suppose the background incidence rate of this is 0.003. The researcher would like to see the sample sizes needed for incidence rates between 0.001 and 0.009 when the power is 90% and the one-sided significance level is 0.025.

## 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 | **0.025** |
| R0 (Background Incidence Rate) | **0.003** |
| D (Additional Incidence Rate) | **0.001 0.003 0.005 0.007 0.009** |

## Annotated Output

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

### Numeric Results

**Numeric Results**

Alternative Hypothesis: One-Sided

| Power | Sample Size N | Background Incidence Rate R0 | Additional Incidence Rate D | Alpha |
|---|---|---|---|---|
| 0.9000 | 35496 | 0.00300 | 0.00100 | 0.0250 |
| 0.9000 | 4744 | 0.00300 | 0.00300 | 0.0250 |
| 0.9000 | 1971 | 0.00300 | 0.00500 | 0.0250 |
| 0.9000 | 1132 | 0.00300 | 0.00700 | 0.0250 |
| 0.9000 | 758 | 0.00300 | 0.00900 | 0.0250 |

**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.

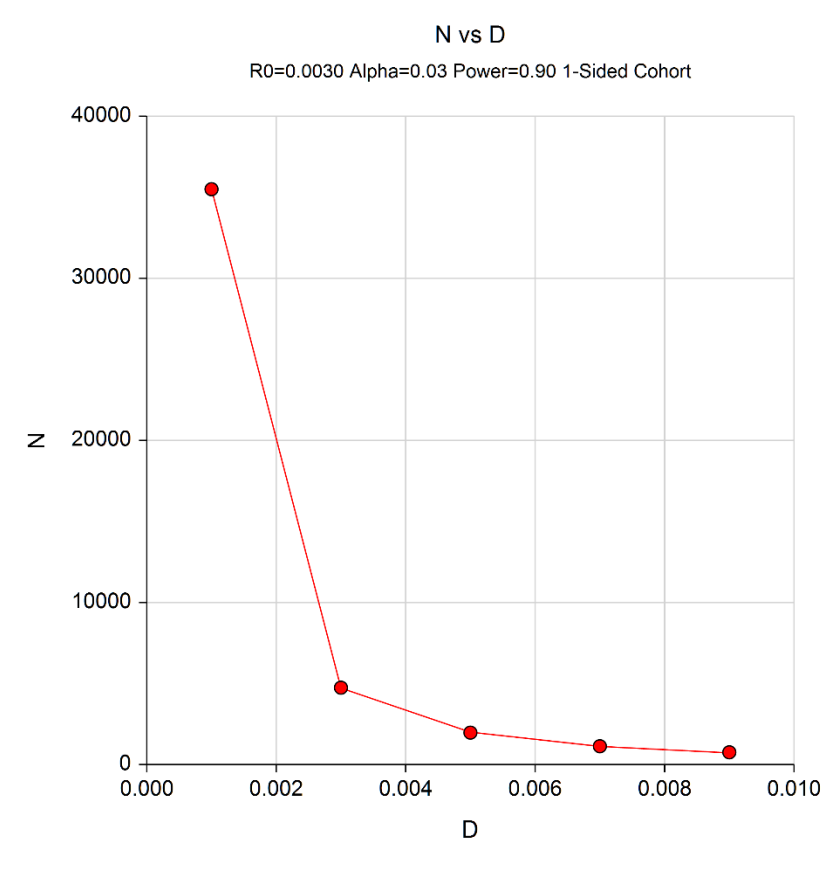
# Tests for One Poisson Rate with Known Background Incidence (Post-Marketing Surveillance)

**Report Definitions**
Power is the probability of rejecting a false null hypothesis.
N is the number of patients monitored.
R0 is the background (existing) incidence rate of adverse reactions.
D is the additional incidence rate of adverse reactions caused by the drug under study.
Alpha is the probability of rejecting a true null hypothesis.

**Summary Statements**
In a cohort study with a known background incidence rate of 0.00300 of a particular adverse reaction, a sample of 35496 patients achieves 90% power to detect an additional incidence rate of 0.00100 when alpha is 0.025.

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

## Plots Section




This plot shows the required sample size at various incidence rates.

# 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 | **0.025** |
| R0 (Background Incidence Rate) | **0.003** |
| D (Additional Incidence Rate) | **0.001 0.003 0.005 0.007 0.009** |

## Output

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

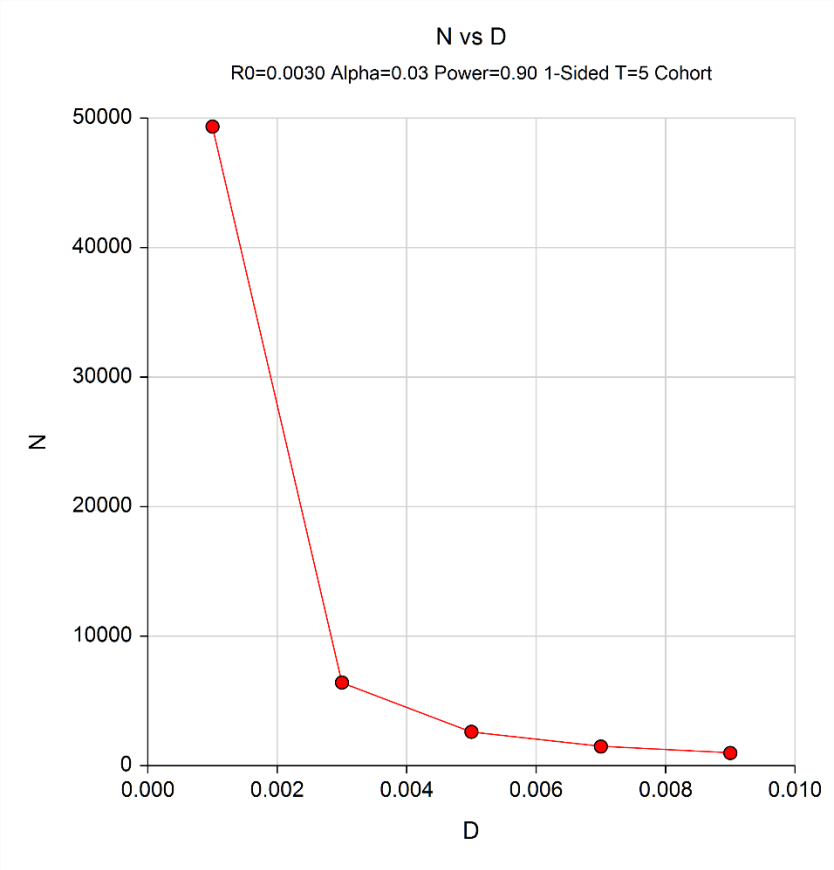
### Numeric Results

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

| Power | Sample Size N | Background Incidence Rate R0 | Additional Incidence Rate D | Alpha | Bonferroni-Corrected Alpha Alpha/T |
|---|---|---|---|---|---|
| 0.9000 | 49345 | 0.00300 | 0.00100 | 0.025 | 0.005000 |
| 0.9000 | 6419 | 0.00300 | 0.00300 | 0.025 | 0.005000 |
| 0.9000 | 2615 | 0.00300 | 0.00500 | 0.025 | 0.005000 |
| 0.9000 | 1479 | 0.00300 | 0.00700 | 0.025 | 0.005000 |
| 0.9000 | 978 | 0.00300 | 0.00900 | 0.025 | 0.005000 |

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 35,496 in Example 1 to 49,345 now. This is an increase of 39%.

## Plots Section




This plot shows the required sample size at various incidence rates.

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

Machin *et al.* (2018) page 91 gives an example of a cohort design with known background incidence R0 is 0.01, D is 0.005, power is 90%, and the alpha level of a one-sided test is 0.05. The computed sample size is 4133.3 = 4134.

## 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** |
| 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 | Sample Size N | Background Incidence Rate R0 | Additional Incidence Rate D | Alpha | Beta |
|---|---|---|---|---|---|
| 0.9000 | 4133 | 0.01000 | 0.00500 | 0.0500 | 0.1000 |

PASS calculates the sample size at 4133 which is accurate to within rounding of 4133.3.