

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 α and power $1 - \beta$, the relationship between these parameters is

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

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

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..... **0.025**
 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 Reports

Numeric Results

Solve For: Sample Size
 Alternative Hypothesis: One-Sided

| Power | Sample Size N | Incidence Rate | | Alpha |
|-------|------------------|------------------|-----------------|-------|
| | | Background R0 | Additional D | |
| 0.9 | 35496 | 0.003 | 0.001 | 0.025 |
| 0.9 | 4744 | 0.003 | 0.003 | 0.025 |
| 0.9 | 1971 | 0.003 | 0.005 | 0.025 |
| 0.9 | 1132 | 0.003 | 0.007 | 0.025 |
| 0.9 | 758 | 0.003 | 0.009 | 0.025 |

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

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Summary Statements

In a study involving a population with a known background incidence rate for a specific adverse reaction of 0.003, a single-group, post-marketing surveillance, cohort design will be used to determine whether application of the new treatment increases the adverse reaction incidence rate. A one-sided test will be used. To detect an additional incidence rate of 0.001 with 90% power and a Type I error rate (α) of 0.025, 35496 subjects will be needed.

Dropout-Inflated Sample Size

| Dropout Rate | Sample Size N | Dropout- Inflated Enrollment Sample Size N' | Expected Number of Dropouts D |
|--------------|------------------|---|--|
| 20% | 35496 | 44370 | 8874 |
| 20% | 4744 | 5930 | 1186 |
| 20% | 1971 | 2464 | 493 |
| 20% | 1132 | 1415 | 283 |
| 20% | 758 | 948 | 190 |

| | |
|--------------|---|
| 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. |
| N | The evaluable sample size at which power is computed. If N subjects are evaluated out of the N' subjects that are enrolled in the study, the design will achieve the stated power. |
| N' | The total number of subjects that should be enrolled in the study in order to obtain N evaluable subjects, based on the assumed dropout rate. After solving for N, N' is calculated by inflating N using the formula $N' = N / (1 - DR)$, with N' always rounded up. (See Julious, S.A. (2010) pages 52-53, or Chow, S.C., Shao, J., Wang, H., and Lohknygina, Y. (2018) pages 32-33.) |
| D | The expected number of dropouts. $D = N' - N$. |

Dropout Summary Statements

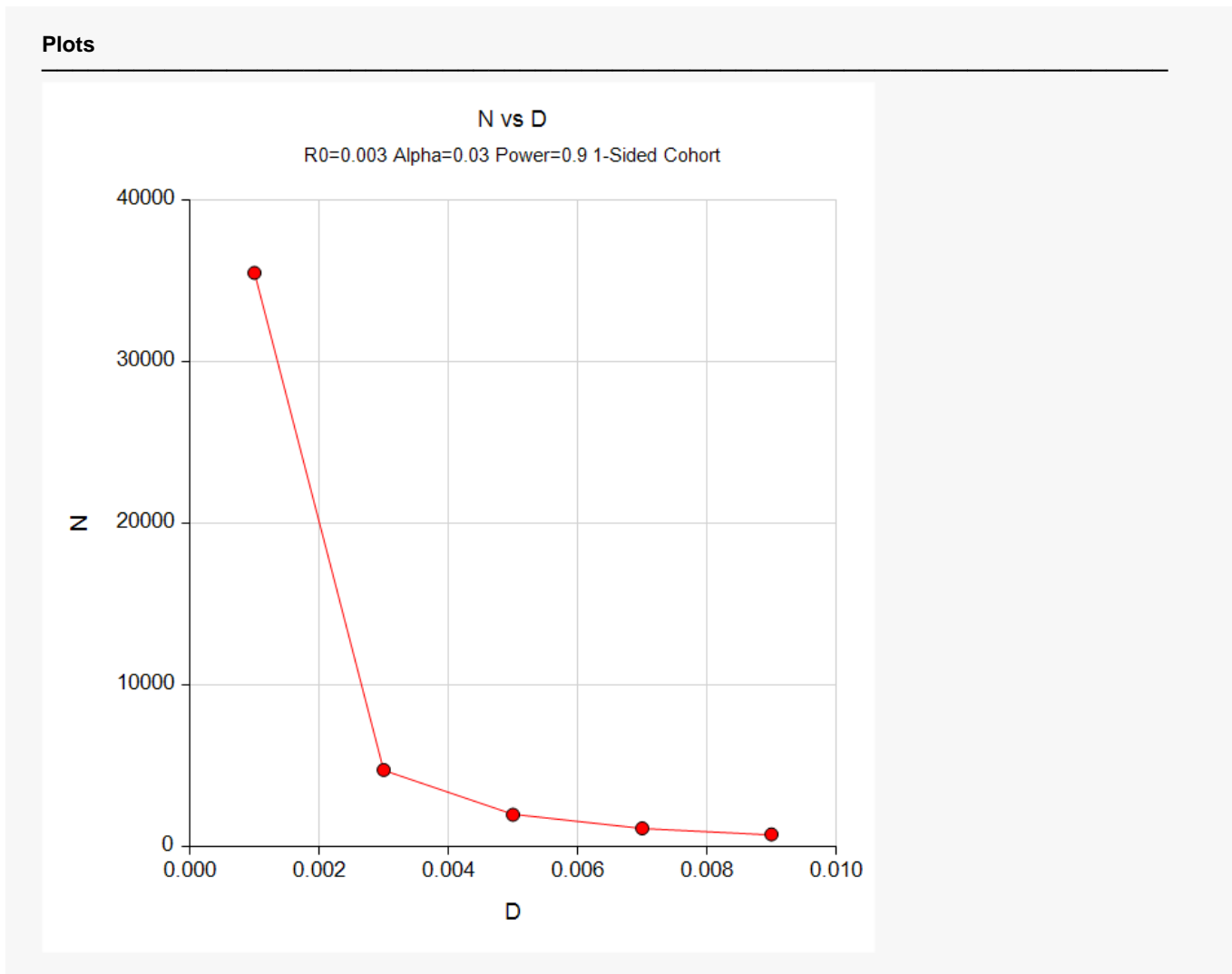
Anticipating a 20% dropout rate, 44370 subjects should be enrolled to obtain a final sample size of 35496 subjects.

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



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

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..... | 0.025 |
| 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.

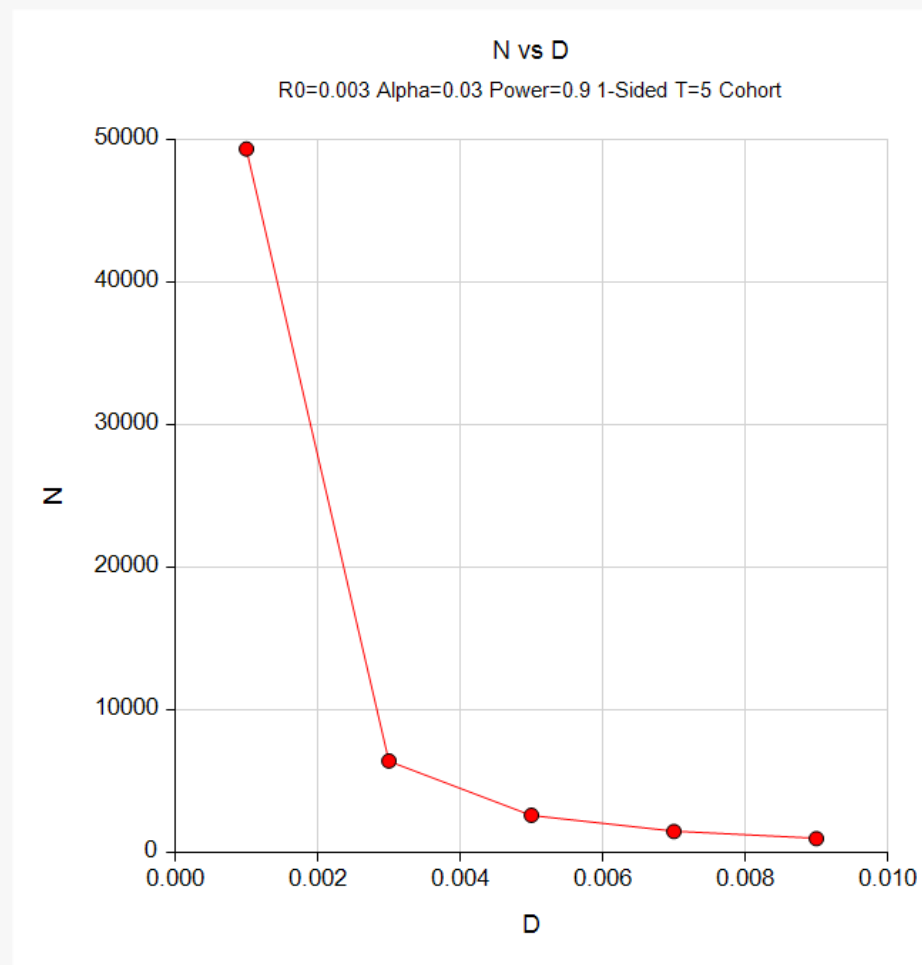
Numeric Reports

| Numeric Results | | | | | |
|----------------------------------|------------------|-----------------------------|-----------------|-------|--|
| Solve For: | | Sample Size | | | |
| Alternative Hypothesis: | | One-Sided | | | |
| T (Adverse Reactions Monitored): | | 5 | | | |
| Power | Sample Size N | Incidence Rate | | Alpha | Bonferroni-Corrected Alpha Alpha/T |
| | | Background R0 | Additional D | | |
| 0.9 | 49345 | 0.003 | 0.001 | 0.025 | 0.005 |
| 0.9 | 6419 | 0.003 | 0.003 | 0.025 | 0.005 |
| 0.9 | 2615 | 0.003 | 0.005 | 0.025 | 0.005 |
| 0.9 | 1479 | 0.003 | 0.007 | 0.025 | 0.005 |
| 0.9 | 978 | 0.003 | 0.009 | 0.025 | 0.005 |

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

Plots



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 R_0 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

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 |
| R_0 (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 | | | |
| | Incidence Rate | | | |
| Power | Sample Size N | Background R_0 | Additional D | Alpha |
| 0.9 | 4133 | 0.01 | 0.005 | 0.05 |

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