

Chapter 814

Reference Intervals for Normal Data

Introduction

This routine calculates the sample size needed to obtain a specified relative width of a confidence interval about the limits of a reference interval calculated from normally distributed data.

Consider a measurement made on a population of individuals (usually healthy patients). A **reference interval** (RI) of this measurement gives the boundaries between which a typical measurement is expected to fall. When a measurement occurs that is outside these reference interval boundaries, there is cause for concern. That is, the measurement is unusually high or low. The reference interval is often presented as percentiles of a reference population, such as the 2.5th percentile and the 97.5th percentile. Of course, the choice of the reference population is important and you would expect that there is often differences according to age, size, and so on. Hence, the population must be partitioned into homogeneous subpopulations and individual reference intervals determined for each.

This procedure calculates sample sizes based on the methods shown in Harris and Boyd (1995), Horn and Pesce (2005), and Machin, Campbell, Tan, and Tan (2018).

Technical Details

Reference Interval

Assume that a sample of N observations of a normally distributed random value Y are summarized by their mean and standard deviation. The $100(1 - \alpha)\%$ *reference interval* is given by the *reference limits* R_L and R_U

where

$$R_L = \bar{y} - cs\sqrt{(N+1)/N} \text{ and } R_U = \bar{y} + cs\sqrt{(N+1)/N}.$$

The *critical value* c is obtained from the t distribution or the normal distribution as $c = t_{N-1, 1-\frac{\alpha}{2}}$ or $c = z_{1-\frac{\alpha}{2}}$, respectively.

The width of this interval is

$$W_{RI} = 2cs\sqrt{(N+1)/N}.$$

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Confidence Intervals of Reference Limits

Each of the reference limits are data estimates of population parameters, so they can be estimated by confidence intervals. These $100(1 - \gamma)\%$ CIs are

$$R_L - z_{1-\frac{\gamma}{2}}SE(R_L) \text{ and } R_L + z_{1-\frac{\gamma}{2}}SE(R_L)$$

$$R_U - z_{1-\frac{\gamma}{2}}SE(R_U) \text{ and } R_U + z_{1-\frac{\gamma}{2}}SE(R_U)$$

where

$$SE(R_L) = SE(R_U) = s\sqrt{(2 + c^2)/2N}$$

The width of these intervals is

$$W_{CI} = 2z_{1-\frac{\gamma}{2}}s\sqrt{(2 + c^2)/2N}.$$

Relative Margin of Error

The ratio of the widths of these intervals is used as a basis for determining the sample size. This ratio is called the relative percentage margin of error and is calculated as

$$ME = 100 W_{CI}/W_{RI}.$$

This is called the relative margin of error because the s cancels out of the ratio.

Hence, the sample size is selected to obtain a specified value of ME .

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 (sample size or margin of error) to be solved for from the other parameters.

Reference Interval Distribution**Reference Interval Distribution**

Specify whether the t or the normal distribution is used to create the reference interval.

Student's-t Distribution

The t distribution adjusts for the sample size. This adjustment is usually used for smaller (less than 100) N's. It will often result in slightly smaller values for N.

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Normal Distribution

The normal distribution is often used because at the N's recommended for reference intervals, there is very little difference between it and the t.

Percentage of the Population in the Reference Interval

RI (Reference Interval Percentage)

Enter one or more values of the reference interval percentage. This is the percentage of data values that are anticipated to fall between the estimated reference limits assuming a normal distribution.

Recommended

Usually, this value is set at 95. Additionally, 90 and 99 are also used.

Range

$0 < RI < 100$.

Percentage Confidence Level of the CI of the RI

CL (Confidence Level Percentage)

Enter one or more values of the confidence level percentage. This is the confidence level (γ) of the confidence interval made for each reference limit.

Recommended

Usually, this value is set to 90.

Range

$50 < CL < 100$.

Relative Margin of Error – Percentage that CI Width is of RI Width

ME (Percentage Margin of Error)

The margin of error is the ratio of the width of the confidence interval about the reference limit of interest to the width of the reference interval.

This ratio is expressed as a percentage. That is, the actual ratio is multiplied by 100.

Sample Size

N (Sample Size)

Enter one or more values for the sample size. This is the number of individuals selected at random from the population to be in the study. For reference interval studies, authors recommend a minimum of 80, or even 120, subjects.

You can enter a single value, a list of values, or a range of values.

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Example 1 – Calculating Sample Size

Suppose a study is being planned to obtain 90%, confidence intervals of the 95% reference limits of blood pressure (BP) for a certain gender and age range. Sample sizes are need for relative margin of errors from 10% to 30%. The goal is to determine the necessary sample size for each value of the relative margin of error.

Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **Reference Intervals for Normal Data** procedure. You may then make the appropriate entries as listed below, or open **Example 1** by going to the **File** menu of the procedure window and choosing **Open Example Template**.

<u>Option</u>	<u>Value</u>
Design Tab	
Solve For	N (Sample Size)
Reference Interval Distribution	Student's t (Exact)
RI (Reference Interval Percentage).....	95
CL (Confidence Level Percentage)	90
ME (Percentage Margin of Error)	10 20 30

Annotated Output

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

Numeric Results

Numeric Results

Reference Interval Distribution: Student's-t (Exact)

Sample Size	Margin of Error 100 W _{CL} /W _{RI}	Reference Interval Percentage	Confidence Level of the C.I. of the Reference Limits		Relative Width of CL W _{CL}	Relative Width of RI W _{RI}
			RI	CL		
N	ME	RI	CL			
203	10.0	95	90		0.395	3.953
48	20.0	95	90		0.811	4.065
19	29.9	95	90		1.290	4.311

Report Definitions

N is the total sample size of the study.

ME is the margin of error which is a measure of imprecision. It is the percentage that the width of the confidence interval of the reference limits is of the width of the reference interval.

RI is the reference interval percentage. It is the percentage of data values that are anticipated to be between the reference limits assuming a normal distribution.

CL is the confidence level of a confidence interval made for each reference limit. It is a percentage.

W_{CL} is the relative width of the confidence interval made for each reference limit. It ignores the value of the standard deviation.

W_{RI} is the relative width of the reference interval. It ignores the value of the standard deviation.

References

Harris, E.K. and Boyd, J.C. 1995. 'Statistical Bases of Reference Values in Laboratory Medicine'. Marcel Dekker. New York, New York.

Horn, P.S. and Pesce, A.J. 2005. 'Reference Intervals - A User's Guide'. AACC Press. Washington D.C.

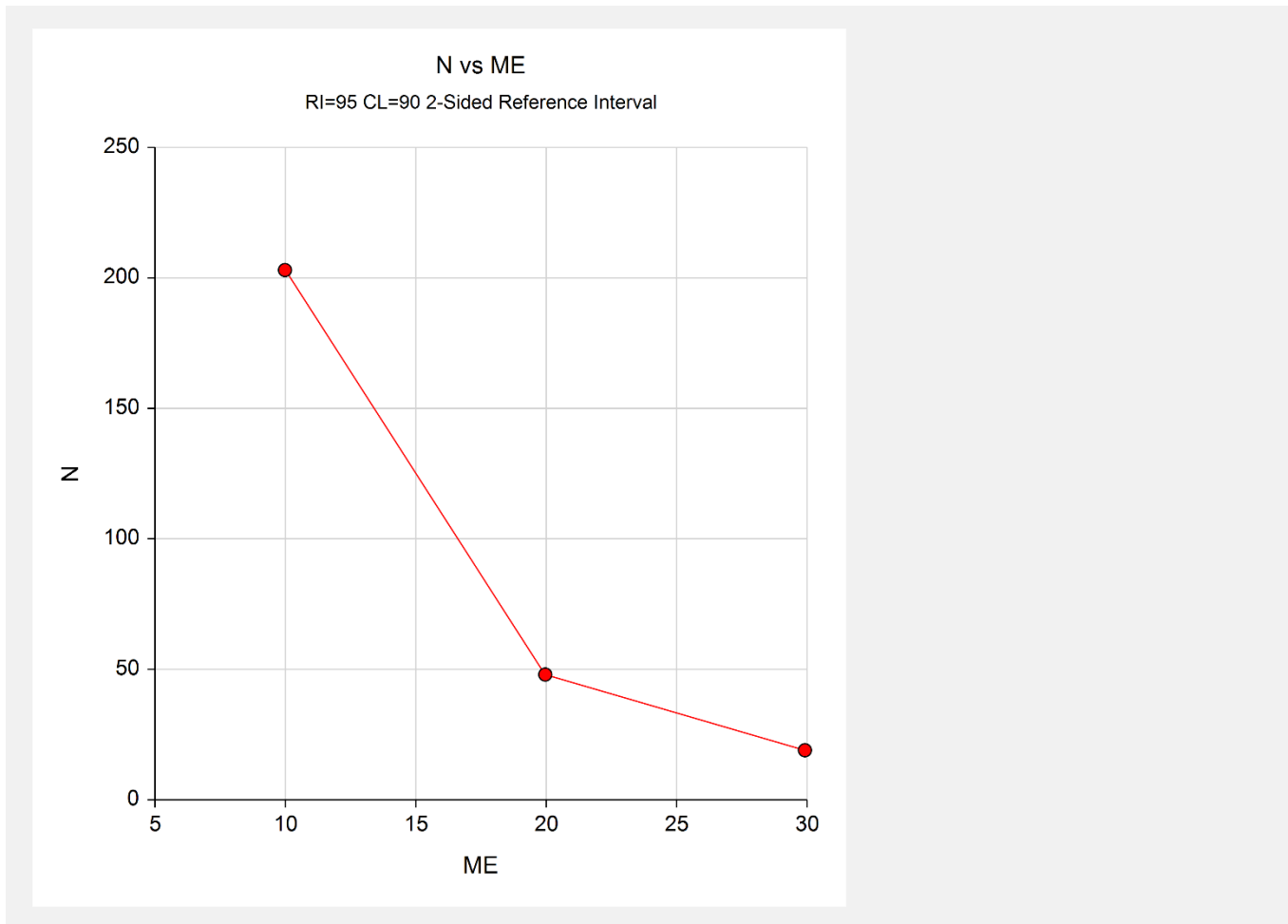
Machin, D, Campbell, M.J., Tan, S.B, Tan, S.H. 2018. 'Sample Sizes for Clinical, Laboratory and Epidemiology Studies, Fourth Edition'. John Wiley and Sons. Hoboken, New Jersey.

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Summary Statements

A sample size of 203 produces two-sided 90% confidence intervals of the two limits of a 95% reference interval. The relative width of each of the confidence intervals is 0.395. The relative width of the reference interval is 3.953. The ratio of these widths multiplied by 100 is 10.0. This is called the margin of error. The reference interval is based on the Student's t distribution.

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

Plots Section

This plot shows the sample size versus the margin of error (ME).

Example 2 – Validation using Harris and Boyd (1995)

Harris and Boyd (1995) page 69 give an example of a study planned to obtain 90% confidence intervals for the 95% reference limits. They calculate the sample size for a relative margin of error of 20% assuming the reference interval uses the normal distribution. They obtain a sample size value of 51.4.

Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **Reference Intervals for Normal Data** procedure. You may then make the appropriate entries as listed below, or open **Example 2** by going to the **File** menu of the procedure window and choosing **Open Example Template**.

<u>Option</u>	<u>Value</u>
Design Tab	
Solve For	N (Sample Size)
Reference Interval Distribution	Normal (Approximate)
RI (Reference Interval Percentage).....	95
CL (Confidence Level Percentage)	90
ME (Percentage Margin of Error)	20

Output

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

Numeric Results

Numeric Results						
Reference Interval Distribution: Normal (Approximate)						
Sample Size	Margin of Error 100 WCL/WRI	Reference Interval Percentage RI	Confidence Level of the C.I. of the Reference Limits CL	Relative Width of CL WCL	Relative Width of RI WRI	
51	19.9	95	90	0.787	3.958	

PASS also calculates the sample size to be 51 which is within rounding of the 51.4 calculated by Harris and Boyd (1995).