Chapter 576

Exact Method for Assessing Agreement in Method Comparison Studies

Introduction

This procedure provides sample size and power calculations for a method comparison study that is analyzed using the exact method proposed by Shieh (2019). This exact method has been shown to have better test characteristics than the common the Bland – Altman (1986) method.

A method comparison study is used to compare two measurement methods. The data consists of pairs of measurements taken on *N* subjects. This exact technique forms two limits of agreement from the *N* paired differences using a special distribution function. Next, these limits are compared to an allowable range which is defined as –δ to δ. If the minimum and maximum values are both between this allowable range, the null hypothesis of disagreement is rejected in favor of the alternative hypothesis that the two measurements are in agreement.

Technical Details

Suppose two measurements (X and Y) are obtained using two measurement methods on each of *N* subjects drawn from a population of interest. It is assumed that the differences computed on these data pairs are normally distributed with constant mean and variance.

Test

The analysis proceeds as follows.

1. Form the *N* paired differences $d_i = x_i - y_i$. These differences are assumed to follow the normal distribution with mean μ and standard deviation σ.

   Define the 100*p*th percentile of the paired differences as $\theta_p = \mu + z_p\sigma$ where z_p is determined from the standard normal distribution.

   To establish agreement between the two methods, the central portion of the distribution of d_i needs to be within a close range about zero. This is accomplished using two percentiles θ_p and θ_{1-p}. The resulting statistical hypotheses are

$$H_0: \theta_{1-p} \leq -\delta \quad \text{or} \quad \delta \leq \theta_p$$

$$H_1: -\delta < \theta_{1-p} \leq -\delta \quad \text{and} \quad \theta_p < \delta$$

2. The bounds $-\delta$ and δ are determined so that the central portion of the distribution of the differences is equal to $P_1^* = 2p - 1$. This requires that the bounds be chosen so that $\Phi[(\delta - \mu)/\sigma] - \Phi\left[\frac{(-\delta-\mu)}{\sigma}\right] > P_1^*$, where $\Phi[z]$ is the cdf of the standard normal distribution. This inequality changes to an equality when $\left(\theta_{1-p}, \theta_p\right) = (-\delta, \delta)$. Hence, there is a one-to-one relationship between P_1^* and δ based on the normal distribution.
3. Compute the mean $\bar{D}$ and the standard deviation SD of these differences using the usual formulas.
4. Form a pair of exact confidence limits B_L and B_U. These confidence limits are

$$B_L = \bar{D} - c_{1-\alpha}\left(SD/\sqrt{N}\right)$$

$$B_U = \bar{D} + c_{1-\alpha}\left(SD/\sqrt{N}\right)$$

The critical value of $c_{1-\alpha}$ is chosen to control the Type I error rate using the definition

$$\Pr\{\theta_{1-p} \le B_L \text{ and } B_U \le \theta_p\} = \alpha$$

A special algorithm to compute this critical value is given by Shieh (2019).

5. Compare the confidence limits B_L and B_U to the bounds $-\delta$ and δ. If $-\delta < B_L < B_U < \delta$ the null hypothesis of disagreement is rejected in favor of the alternative hypothesis that the two measurement methods are in agreement.

Power Analysis

The exact power of this testing procedure is given in Shieh (2019). It requires numeric integration, and the extensive details will not be repeated here. This power formula requires the specification of *N*, the null central portion P_0^*, the alternative central portion P_1^* or the corresponding bound δ, the significance level α, and μ and σ.

If the sample size is required, this power formula can be used in a binary search.

Example 1 – Finding the Sample Size

Clinicians wish to conduct a method comparison study and analyze it with the exact agreement test. They want to estimate the number of subjects that must be measured significance level is 0.05, P0* is 0.95, the power is 0.8 or 0.9, δ is 7, the mean of the paired differences is 0.5 and standard deviation between 2.5 and 2.7.

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 ..... **N (Number of Pairs)**
Power..... **0.8 0.9**
Alpha..... **0.05**
P0* (Central Portion|H0) **0.95**
δ or P1* Input..... **Enter δ and calculate P1***
δ (Difference Bound)..... **7**
μ (Mean of Differences) **0.5**
σ (Std Dev of Differences) **2.5 2.6 2.7**

Output

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

Numeric Reports

Numeric Results

Solve For: N (Number of Pairs)
Hypotheses: H0: Methods Disagree, Central Portion Not Within Tolerance
H1: Methods Agree, Central Portion Within Tolerance

		Central Portion		Paired Differences				
Power	Number of Pairs N	H0 (Null) P0*	H1 (Actual) P1*	Bound δ	Mean μ	Standard Deviation σ	Alpha α	Critical Value C[1 - α]
0.8018	34	0.95	0.9940	7	0.5	2.5	0.05	13.5705
0.8028	45	0.95	0.9918	7	0.5	2.6	0.05	15.2082
0.8034	62	0.95	0.9892	7	0.5	2.7	0.05	17.4196
0.9016	48	0.95	0.9940	7	0.5	2.5	0.05	15.6231
0.9004	64	0.95	0.9918	7	0.5	2.6	0.05	17.6602
0.9020	90	0.95	0.9892	7	0.5	2.7	0.05	20.5142

Power The probability of rejecting a false null hypothesis when the alternative hypothesis is true.
N The number of subject pairs. That is, each subject produces two measurements, one for each method.
P0* The target central portion of the distribution of paired differences assumed by the null hypothesis, H0.
P1* The actual central portion of the distribution of paired differences assumed by the alternative hypothesis, H1.
δ The magnitude of the difference boundaries. The null hypothesis is that the target central portion of the distribution of paired differences falls within the interval [-δ, δ].
μ The population mean of the sample differences.
σ The population standard deviation of the sample differences.
Alpha The probability of rejecting a true null hypothesis.
C[1 - α] The critical value used to construct the confidence interval of the data.

Summary Statements

A paired (two-measurement) design will be used to test agreement of two measurement methods (e.g., assays) using an exact test of method agreement (Shieh, 2019). Each subject will be measure twice, once with each measurement method. The test will be performed by comparing the specified difference bounds (forming the allowable range) to the two limits of agreement. If the limits of agreement (as calculated from the paired differences) are within the allowable range, the null hypothesis is rejected and the conclusion of method agreement is reached. A Type I error rate (α) of 0.05 will be used. The target central portion of the distribution of paired differences within the allowable range under the null hypothesis is assumed to be 0.95. The assumed central portion of the distribution of paired differences within the allowable range is 0.994, and this corresponds to the difference bounds (allowable range) of [-7, 7]. The mean of the sample differences is anticipated to be 0.5 and standard deviation of the sample differences is anticipated to be 2.5. With these parameters, to obtain a power (to detect agreement) of 80%, 34 subject pairs will be needed.

Dropout-Inflated Sample Size

Dropout Rate	Sample Size N	Dropout-Inflated Enrollment Sample Size N'	Expected Number of Dropouts D
20%	34	43	9
20%	45	57	12
20%	62	78	16
20%	48	60	12
20%	64	80	16
20%	90	113	23

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 Lokhnygina, Y. (2018) pages 32-33.)
D The expected number of dropouts. D = N' - N.

Dropout Summary Statements

Anticipating a 20% dropout rate, 43 subjects should be enrolled to obtain a final sample size of 34 subjects.

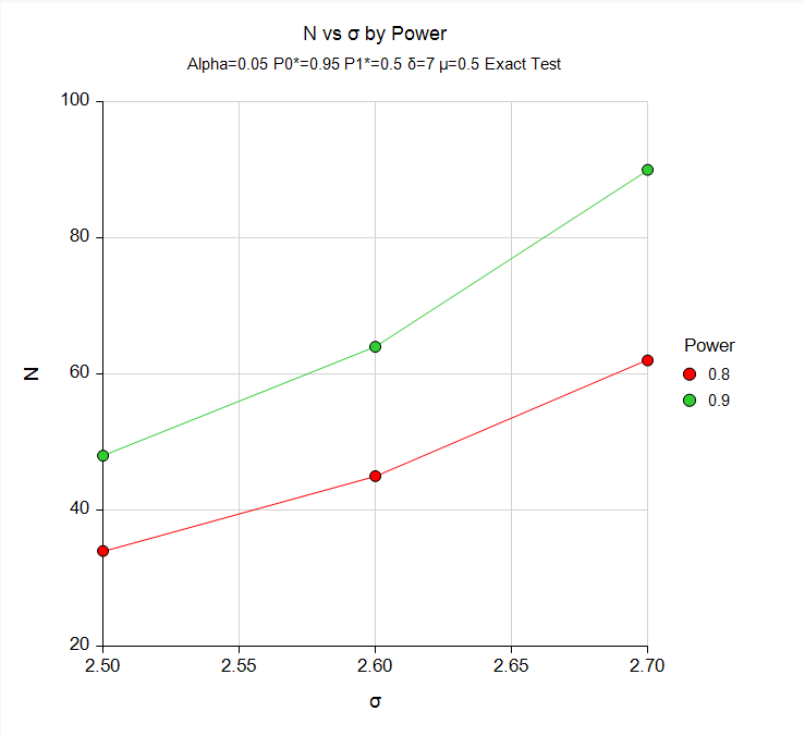
References

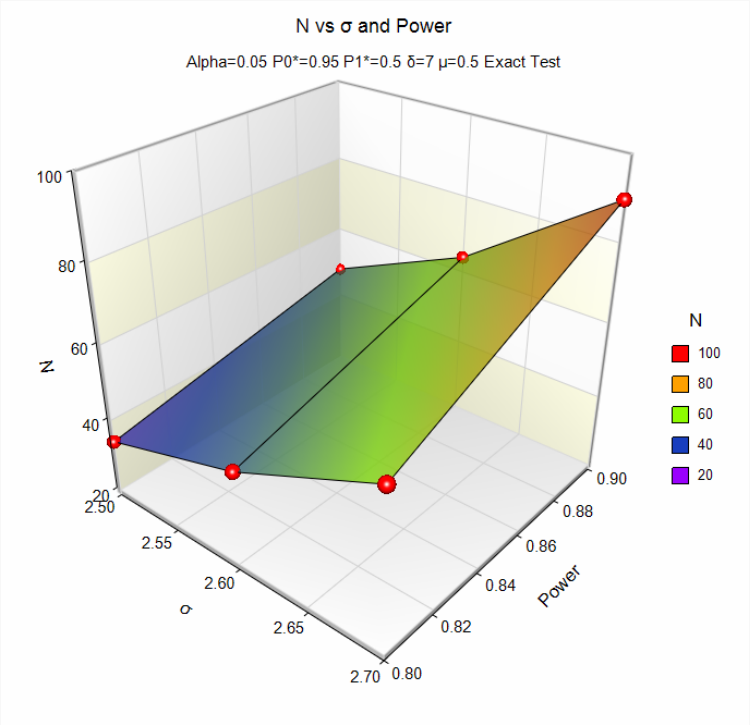
Shieh, Gwowen. 2019. Assessing Agreement between Two Methods of Quantitative Measurements: Exact Test Procedure and Sample Size Calculation.' Statistics in Biopharmaceutical Research. Link: https://doi.org/10.108/19466315.2019.1677495.
Bland, J.M., Altman, D.G. 1986. 'Statistical methods for assessing agreement between two methods of clinical measurement.' The Lancet i:307-310.

These reports show the values of each of the parameters, one scenario per row.

Plots Section

Plots





These plots show the relationship between the standard deviation and sample size for the two alpha levels.

Example 2 – Validation using Shieh (2019)

Shieh (2019) provides an example on page 6 that we will use to validate the program. They want to estimate the number of subjects that must be measured significance level is 0.05, P0* is 0.8, the power is 0.8 or 0.9, δ is 7, the mean of the paired differences is 0.5 and standard deviation between 2.5 and 2.7. The article reports sample sizes of 14 and 20.

We will compute the power for a range of N's from 200 to 203.

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 ..... **N (Number of Pairs)**
Power..... **0.8 0.9**
Alpha..... **0.05**
P0* (Central Portion|H0) **0.8**
δ or P1* Input..... **Enter δ and calculate P1***
δ (Difference Bound)..... **0.1**
μ (Mean of Differences) **0.011**
σ (Std Dev of Differences) **0.044**

Output

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

Numeric Results

Solve For: N (Number of Pairs)
Hypotheses: H0: Methods Disagree, Central Portion Not Within Tolerance
H1: Methods Agree, Central Portion Within Tolerance

		Central Portion		Paired Differences				
Power	Number of Pairs N	H0 (Null) P0*	H1 (Actual) P1*	Bound δ	Mean μ	Standard Deviation σ	Alpha α	Critical Value C[1 - α]
0.8079	14	0.8	0.9726	0.1	0.011	0.044	0.05	6.2512
0.9112	20	0.8	0.9726	0.1	0.011	0.044	0.05	7.0605

PASS also shows the sample sizes to be 14 and 20, thus validating the procedure.