

Chapter 481

Tests for Two Means in a Multicenter Randomized Design

Introduction

In a multicenter design with a continuous outcome, a number of centers (e.g. hospitals or clinics) are selected at random from a population of centers. The subjects in each center are then randomized to either of two treatments.

The data are analyzed using a mixed effects model that includes a fixed treatment effect and a random center effect. The test of interest is the F-test of the treatment effect. This is a two-sided test of the hypothesis that there is no treatment effect. Note that the treatment-by-center interaction is not included in this model, although it could be in a secondary analysis.

Technical Details

These results come from Vierron and Giraudeau (2007). Consider a mixed effect model for a two-way layout (treatment and class) without interaction.

$$Y_{ijk} = \mu + \delta_i + C_j + \varepsilon_{ijk} \quad i = 1, 2, \quad j = 1, \dots, Q, \quad k = 1, \dots, n$$

where Y_{ijk} is the (continuous) response of the k th subject, receiving the i th treatment in the j th center. The overall response is μ . The treatment effects δ_1 and δ_2 are fixed constants where $\delta_1 = \delta/2$ and $\delta_2 = -\delta/2$. Hence, the two treatment means are $\mu_1 = \mu + \delta/2$ and $\mu_2 = \mu - \delta/2$, so that $\delta = \mu_1 - \mu_2$.

The class effects C_j are random, distributed normally with mean zero and variance σ_C^2 . The errors ε_{ijk} are distributed normally with a mean of zero and a variance of σ_ε^2 . It is assumed that the errors and the class effects are independent. The authors make the simplifying assumption that the sample size from all centers are equal to $2n$ and that the number of subjects assign to each treatment is the same. Thus the total sample size N is $2Qn$. Note that the authors conduct a number of simulation studies and conclude that when the assumptions of equal class size and equal treatment size are violated, their results are still very close.

In the sample size formula to follow, the center effects are recast as the intraclass correlation coefficient, ρ , which is defined as the proportion of the total variation in Y that is accounted for by the variance in the centers.

Symbolically, ρ (or *ICC*) is defined as

$$\rho = \frac{\sigma_C^2}{\sigma_C^2 + \sigma_\varepsilon^2}$$

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Note that the variance of the responses σ^2 is given by

$$\sigma^2 = \sigma_Y^2 = \sigma_C^2 + \sigma_\varepsilon^2$$

Vierron and Giraudeau (2007) show that for this situation, the power is given by

$$Power = \Phi\left(\frac{\delta\sqrt{N}}{\sigma\sqrt{1-\rho}}\right) - z_{1-\alpha/2}$$

where $\Phi(x)$ is the cumulative standard normal distribution function and z_ϕ is found so that $\phi = \Phi(z_\phi)$.

Note that the power does not depend on the number of centers in the study or their size. The formula makes that assumption that there are several centers and the number of subjects from each center is almost uniform.

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

This option specifies the parameter to be solved for from the other parameters. The parameters that may be selected are *Mean Difference*, *Sample Size*, and *Power*.

Under most situations, you will select *Sample Size*.

Note that the value selected here always appears as the vertical axis on the charts.

The program is set up to evaluate power directly. For the mean difference and sample size, a binary search is made.

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 was used for power. Now, 0.90 is also commonly used.

A single value may be entered or a range of values such as *0.8 to 0.95 by 0.05* may be entered.

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 must be between zero and one. Historically, the value of 0.05 has been used for alpha. This means that about one test in twenty will falsely reject the null hypothesis. 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.

You may enter a single value, such as *0.05*, or a range of values, such as *0.01 0.05 0.10* or *0.01 to 0.10 by 0.01*.

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Sample Size

N (Total Number of Subjects)

Enter the total number of subjects found by summing the number in each center.

You may enter a single value, a range of values, or a series of values.

Mean Difference

$\mu_1 - \mu_2$ (Mean Difference)

Specify the mean difference that you want to be able to detect. Note that the scale of this value must match the scale of the standard deviation. When the mean difference is large relative to the standard deviation, the resulting sample size will only detect the differences that are at least as big. When the mean difference is small relative to the standard deviation, a larger sample size is required to detect differences that are smaller than this.

You can enter a single value such as

1

or a range of values such as

1 2 3

or a series of values such as

0.2 to 2 by 0.2.

Standard Deviation and Intraclass Correlation

σ (Response Standard Deviation)

Specify the standard deviation of the response variable across all centers. This value must be on the same scale as the mean differences.

Because the true variance is unknown, it is recommended that a range of values be entered here. Or, you can enter a '1' here and specify the mean difference on a z scale, $(\mu_1 - \mu_2)/\sigma$.

You can enter a single value such as

1

or a range of values such as

1 2 3 4 5

or a series of values such as

2 to 10 by 2.

ρ (Intraclass Correlation, ICC)

The value of ρ , or ICC, is the proportion that the center-to-center variance is of the response variance. The formula is given by

$$\rho = \frac{\sigma_c^2}{\sigma_c^2 + \sigma_e^2} = \frac{\sigma_c^2}{\sigma^2}$$

This value is usually less than 0.15. If you are not sure, use 0.10.

Note that this is a proportion and so it must be positive. You can enter a single value or a range or series of values.

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Example 1 – Calculating Sample Size

Suppose that a study is to be conducted in which $\alpha = 0.05$; power = 0.90; *mean difference* = 0.1, 0.2, or 0.3; $\sigma = 1.0$; and $\rho = 0.1$. Sample size is to be solved for.

Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **Tests for Two Means in a Multicenter Randomized Design** procedure window by expanding **Means**, then **Two Independent Means**, and then clicking on **Multicenter Randomized**, and then clicking **Tests for Two Means in a Multicenter Randomized Design**. 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**.

<u>Option</u>	<u>Value</u>
Design Tab	
Solve For	Sample Size
Power.....	0.90
Alpha.....	0.05
$\mu_1 - \mu_2$ (Mean Difference).....	0.1 0.2 0.3
σ (Response Standard Deviation)	1.0
ρ (Intracluster Correlation).....	0.10

Annotated Output

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

Numeric Results

Numeric Results for Mixed Effects F Test

	Total Sample Size N	Mean Difference $\mu_1 - \mu_2$	Response Standard Deviation σ	Intraclass Correlation Coefficient ρ	Center Standard Deviation σ_c	Error Standard Deviation σ_ϵ	Alpha
Power							
0.9000	3783	0.100	1.000	0.100	0.316	0.949	0.050
0.9001	946	0.200	1.000	0.100	0.316	0.949	0.050
0.9005	421	0.300	1.000	0.100	0.316	0.949	0.050

References

- Vierron, E. and Giraudeau, B. 2007. 'Sample size calculation for multicenter randomized trial: Taking the center effect into account.' *Contemporary Clinical Trials*, Vol 28. Pages 451-458.
- Vierron, E. and Giraudeau, B. 2009. 'Design effect in multicenter studies: gain or loss of power?' *BMC Medical Research Methodology*, 9:39. This article is available from www.biomedcentral.com/1471-2288/9/39

Report Definitions

- Power is the probability of rejecting a false null hypothesis. It should be close to one.
- N is the number of subjects in either group in all centers.
- Mean Difference $\mu_1 - \mu_2$ is difference between the group means at which the power is calculated.
- Response Standard Deviation σ is standard deviation of the response variable.
- Intraclass Correlation Coefficient ρ is the proportion that the center-to-center variance is of the response variance.
- Center Standard Deviation σ_c is the square root of the center-to-center variance.
- Error Standard Deviation σ_ϵ is the square root of the subject-to-subject variance calculated within a center.
- Alpha is the probability of rejecting a true null hypothesis.

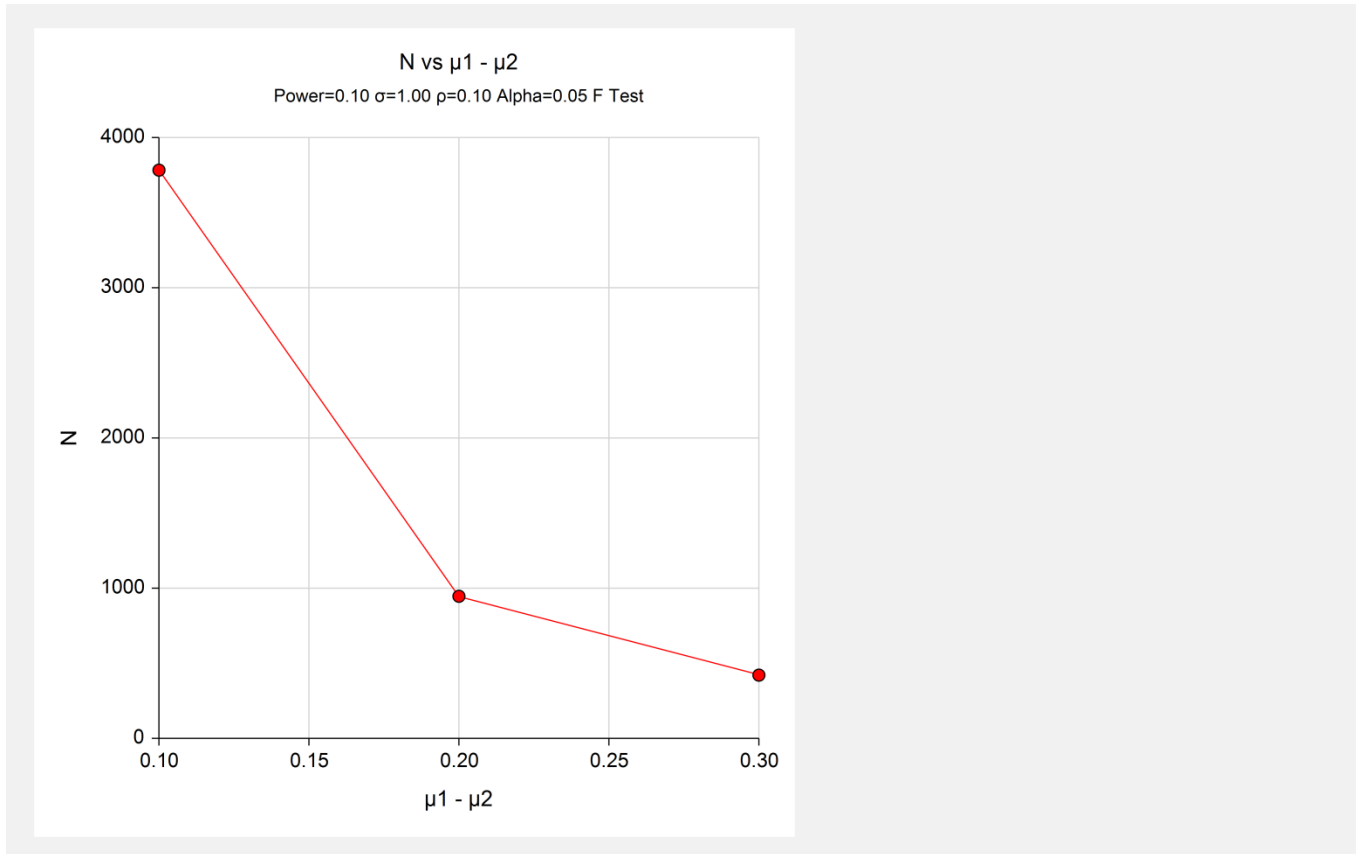
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Summary Statements

A sample size of 3783 achieves 90% power to detect a difference of 0.100 between the two means when the standard deviation of the response variable is 1.000 and the intraclass correlation (ρ) is 0.100 using a test with a significance level of 0.050 obtained from a mixed effects model fit without the treatment-by-center interaction.

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

Plots Section



This plot shows the sample size versus the difference in means.

Example 2 – Validation using Vierron and Giraudeau

Vierron and Giraudeau (2007) page 454, Table 2 gives $N = 302$ when $\alpha = 0.05$; $\text{power} = 0.80$; $\text{mean difference} = 0.25$; $\sigma = 1.0$; and $\rho = 0.4$.

Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **Tests for Two Means in a Multicenter Randomized Design** procedure window by expanding **Means**, then **Two Independent Means**, and then clicking on **Multicenter Randomized**, and then clicking **Tests for Two Means in a Multicenter Randomized Design**. 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**.

<u>Option</u>	<u>Value</u>
Design Tab	
Solve For	Sample Size
Power.....	0.80
Alpha.....	0.05
$\mu_1 - \mu_2$ (Mean Difference).....	0.25
σ (Response Standard Deviation)	1.0
ρ (Intracluster Correlation)	0.40

Annotated Output

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

Numeric Results

Numeric Results for Mixed Effects F Test							
	Total Sample Size	Mean Difference $\mu_1 - \mu_2$	Response Standard Deviation σ	Intraclass Correlation Coefficient ρ	Center Standard Deviation σ_c	Error Standard Deviation σ_ϵ	Alpha
Power	N						
0.8008	302	0.250	1.000	0.400	0.632	0.775	0.050

PASS also calculates the sample size to be 302.