

Chapter 595

Williams' Test for the Minimum Effective Dose

Introduction

The biological activity (i.e. toxicity) of a substance may be investigated by experiments in which the treatments are a series of monotonically increasing (or decreasing) doses of the substance. One of the aims of such a study is to determine the minimum effective dose (the lowest dose at which there is activity). Williams (1971, 1972) describes such a test. Chow et al. (2008) give the details of performing a power analysis and sample size calculation of this test.

Test Procedure

This section will summarize the Williams' test procedure. Those needing more details should look at Williams (1971, 1972).

Suppose that a set of treatments are comprised of a control (treatment 0) and K dose levels of substance of interest (treatments $i = 1, \dots, K$). All treatment groups have the same sample size n . Assume that the effect of the substance is to increase the mean response and that the mean response is proportional to the size of the dose. That is, assume that

$$\mu_0 \leq \mu_1 \leq \mu_2 \leq \dots \leq \mu_K.$$

The statistical hypothesis that is tested by the Williams' test is

$$H_0: \mu_0 = \mu_1 = \dots = \mu_K \text{ vs. } H_a: \mu_0 = \mu_1 = \dots = \mu_{i-1} < \mu_i \leq \mu_{i+1} \leq \dots \leq \mu_K.$$

The test statistic is given by

$$T_i = \frac{\hat{\mu}_i - \bar{X}_0}{s \sqrt{\frac{1}{n_i} + \frac{1}{n_0}}}$$

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where s is an unbiased estimate of σ , the within group standard deviation that is statistically independent of the \bar{X}_i , and $\hat{\mu}_i$ is the maximum likelihood estimate of μ_i given by

$$\hat{\mu}_i = \max_{1 \leq u \leq i} \min_{i \leq v \leq K} \left\{ \frac{\sum_{j=u}^v n_j \bar{X}_j}{\sum_{j=u}^v n_j} \right\}$$

The null hypothesis of no treatment difference is rejected and the fact that the i th dose level is the minimum effective dose is concluded if

$$T_j > t_{j,\alpha} \text{ for all } j \geq i$$

where $t_{j,\alpha}$ is the upper α th percentile of the distribution of T_j . These critical values were tabulated by Williams (1972) and they are available in PASS using special interpolation routines. The only values of α that are available are 0.05, 0.025, 0.01, and 0.005.

Technical Details

Computing Power

The following approximate function for power is given by Chow et al. (2008) page 288.

$$1 - \beta = 1 - \Phi\left(t_{K,\alpha} - \frac{\Delta}{\sigma\sqrt{2/n}}\right)$$

where Δ is the clinically meaningful minimal difference and $\Phi(z) = \int_{-\infty}^z \text{Normal}(0,1)$.

This can be rearranged to obtain the following expression for n

$$n = \frac{2\sigma^2 [t_{K,\alpha} + z_\beta]^2}{\Delta^2}$$

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 calculated from the values of the other parameters. Under most conditions, you would select either *Power* or *Sample Size*.

Select *Sample Size* when you want to determine the sample size needed to achieve a given power and alpha error level. Select *Power* when you want to calculate the power of an experiment that has already been run.

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.

Alpha

This option specifies a value for the probability of a type-I error. A type-I error occurs when a true null hypothesis is rejected.

Only four values are available: 0.05, 0.025, 0.01, 0.005.

Sample Size

G (Number of Groups)

Select the number of groups in the study (including the control group). Since the experiment compares K doses to a single control (zero dose), there are actually K+1 groups. Values from 3 to 11 are available.

For example, suppose an experiment includes three doses and a control group, you would enter '4' as the total number of groups.

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n (Sample Size per Group)

Enter one or more values for the group sample size (n). This is the number of individuals in each group. The Williams' design assumes that the number of subjects in each group is constant. The total number of subjects is $N = n(G)$.

You may enter a list of values such as

10 20 30 40 50

or

10 to 100 by 10.

Effect Size – Means

Δ (Minimum Detectable Difference)

Enter a value (or range of values) for the minimum difference between the control mean and each of the treatment means that is clinically meaningful. The goal of the study is to find the minimum dose that will cause this difference in response to occur.

Note that this is NOT the difference that you think will occur. It is the minimum that you want to detect.

Range

These values should be positive. You can enter one or more values in a list using the usual syntax. For example, you could enter

1 1.2 1.4

or

1 to 5 by 0.5.

σ (Standard Deviation)

Enter a value (or range of values) for the standard deviation of the responses within a group. The analysis assumes that this standard deviation is constant across all groups. These values must be positive.

You can enter one or more values in a list using the usual syntax. For example, you could enter

1 2 3 4 5

or

1 to 5 by 1.

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Example 1 – Finding the Sample Size

A pharmaceutical company needs to determine the minimum dose of a drug used to treat asthma. A 5-arm design including a placebo control and four active dose levels (0, 10mg, 20mg, 30mg, and 40 mg) of the test drug is planned. The response variable is percent change from baseline FEV1. Previous studies have found that $\sigma = 25\%$. Determine the sample size required to detect a change of at least 10%, 15%, 20%, 30%, 40%, and 50% assuming 90% power and $\alpha = 0.05$.

Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **Williams' Test for the Minimum Effective Dose** procedure window by expanding **Means**, then clicking on **Multiple Comparisons**, and then clicking on **Williams' Test for the Minimum Effective Dose**. 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
G (Number of Groups)	5
Δ (Minimum Detectable Difference)	10 15 20 30 40 50
σ (Standard Deviation)	25

Annotated Output

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

Numeric Results

Numeric Results for Williams' Test

Null Hypothesis: $\mu[0] = \mu[1] = \dots = \mu[K]$

Alternative Hypothesis: $\mu[0] = \mu[1] = \dots = \mu[i-1] < \mu[i] \leq \mu[i+1] \leq \dots \leq \mu[K]$

Power	Number of Groups	Group Sample Size	Total Sample Size	Alpha	Beta	Minimum Detectable Difference	Standard Deviation
	(G)	(n)	(N)			(Δ)	(σ)
0.9021	5	116	580	0.0500	0.0979	10.00	25.00
0.9036	5	52	260	0.0500	0.0964	15.00	25.00
0.9003	5	29	145	0.0500	0.0997	20.00	25.00
0.9187	5	14	70	0.0500	0.0813	30.00	25.00
0.9186	5	8	40	0.0500	0.0814	40.00	25.00
0.9057	5	5	25	0.0500	0.0943	50.00	25.00

References

Chow, S.C.; Shao, J.; Wang, H. 2008. Sample Size Calculations in Clinical Research, Second Edition. Chapman & Hall. New York. Pages 287 - 293.

Williams, D.A. 1971. 'A Test for Differences between Treatment Means When Several Dose Levels are Compared with a Zero Dose Control', Biometrics, Volume 27, No. 1, pages 103-117.

Williams, D.A. 1972. 'The Comparison of Several Dose Levels with a Zero Dose Control', Biometrics, Volume 28, No. 1, pages 519-531.

Williams' Test for the Minimum Effective Dose**Report Definitions**

Power is the probability of rejecting a false null hypothesis.

G is the number of groups.

n is the sample size of each dose level group.

N is the total sample size which is equal to $n(G)$.

Alpha is the probability of rejecting a true null hypothesis.

Beta is the probability of accepting a false null hypothesis.

Δ (delta) is the minimum difference between a treatment mean and the control mean that is to be detected by the study.

σ (sigma) is the standard deviation within each group.

Summary Statements

A total sample size of 580 (or 116 in each of the 5 groups) achieves 90% power to detect a minimal difference of 10.00 between the zero-dose mean and a treatment mean with a significance level (alpha) of 0.0500 and a standard deviation of 25.00 using Williams' Test.

This report shows the values of each of the parameters, one scenario per row. The values of power and beta were calculated from the other parameters.

Power

Power is the probability of rejecting a false null hypothesis.

G

G is the number of groups in the study including a zero-dose control group.

n

n is the sample size of each dose level group.

N

N is the total sample size which is equal to $n(G)$.

Alpha

Alpha is the probability of rejecting a true null hypothesis.

Beta

Beta is the probability of accepting a false null hypothesis.

 Δ (Minimum Detectable Difference)

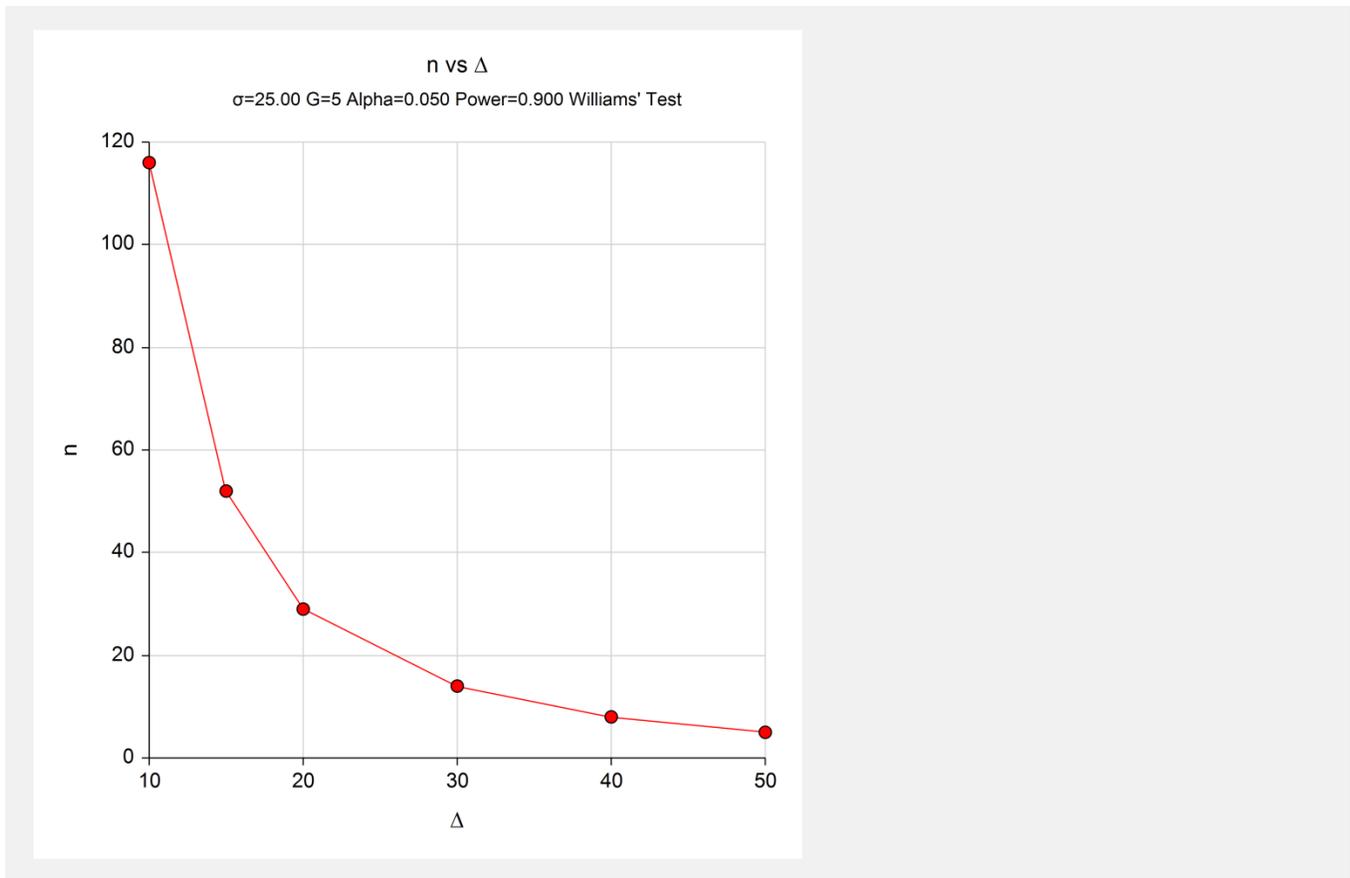
Δ (delta) is the minimum difference between a treatment mean and the control mean that is to be detected by the study.

 σ (Standard Deviation)

σ (sigma) is the standard deviation within each group.

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Plots Section



This plot shows the relationship between the group sample size and the minimal difference.

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Example 2 – Validation using Chow

Chow et al. (2008) page 288 presents an example that we will use to validate this procedure. In this example, $\Delta=11$, $\sigma = 22$, $G = 4$, power = 80%, and $\alpha = 0.05$. Using the formula described earlier, they obtain a group sample size of 53 (actually, 53.7).

Setup

This section presents the values of each of the parameters needed to run this example. First, from the PASS Home window, load the **Williams' Test for the Minimum Effective Dose** procedure window by expanding **Means**, then clicking on **Multiple Comparisons**, and then clicking on **Williams' Test for the Minimum Effective Dose**. 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
G (Number of Groups).....	4
Δ (Minimum Detectable Difference).....	11
σ (Standard Deviation)	22

Output

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

Numeric Results

Numeric Results for Williams' Test							
Null Hypothesis: $\mu[0] = \mu[1] = \dots = \mu[K]$							
Alternative Hypothesis: $\mu[0] = \mu[1] = \dots = \mu[i-1] < \mu[i] \leq \mu[i+1] \leq \dots \leq \mu[K]$							
	Number of Groups (G)	Group Sample Size (n)	Total Sample Size (N)	Alpha	Beta	Minimum Detectable Difference (Δ)	Standard Deviation (σ)
Power	4	54	216	0.0500	0.1975	11.00	22.00

Note that PASS has rounded up to the next integer, while Chow rounded down. Thus, $n = 54$ guarantees a power of at least 80%.