

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

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

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

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

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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.

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

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

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

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**
 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**

Output

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

Numeric Reports

Numeric Results for Williams' Test

Solve For: **Sample Size**
 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 G	Sample Size		Minimum Detectable Difference Δ	Standard Deviation σ	Alpha
		Group n	Total N			
0.9021	5	116	580	10	25	0.05
0.9036	5	52	260	15	25	0.05
0.9003	5	29	145	20	25	0.05
0.9187	5	14	70	30	25	0.05
0.9186	5	8	40	40	25	0.05
0.9057	5	5	25	50	25	0.05

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Power	The probability of rejecting a false null hypothesis when the alternative hypothesis is true.
G	The number of groups.
n	The sample size of each dose level group.
N	The total sample size which is equal to $n(G)$.
Δ	The minimum difference between a treatment mean and the control mean that is to be detected by the study.
σ	The standard deviation within each group.
Alpha	The probability of rejecting a true null hypothesis.

Summary Statements

A minimum effective dose design with 5 groups (one zero-dose control and 4 dose level treatments) will be used to determine the lowest dose at which there is activity (mean difference from the control). The comparison will be made using Williams' Test for minimum effective dose, with a Type I error rate (α) of 0.05. The common within-group standard deviation of responses for all groups is assumed to be 25. To detect a minimum difference of 10 (between the zero-dose control mean and a treatment mean), with 90% power, the needed group sample sizes are 116 (for a total of 580 subjects).

Dropout-Inflated Sample Size

Group	Dropout Rate	Sample Size n	Dropout- Inflated Enrollment Sample Size n'	Expected Number of Dropouts D
1 - 5	20%	116	145	29
Total		580	725	145
1 - 5	20%	52	65	13
Total		260	325	65
1 - 5	20%	29	37	8
Total		145	185	40
1 - 5	20%	14	18	4
Total		70	90	20
1 - 5	20%	8	10	2
Total		40	50	10
1 - 5	20%	5	7	2
Total		25	35	10

Group	Lists the group numbers.
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 for each group 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 number of subjects that should be enrolled in each group 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 in each group. $D = n' - n$.

Dropout Summary Statements

Anticipating a 20% dropout rate, group sizes of 145, 145, 145, 145, and 145 subjects should be enrolled to obtain final group sample sizes of 116, 116, 116, 116, and 116 subjects.

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References

- Chow, S.C., Shao, J., and 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.
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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 $n(G)$.

 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)

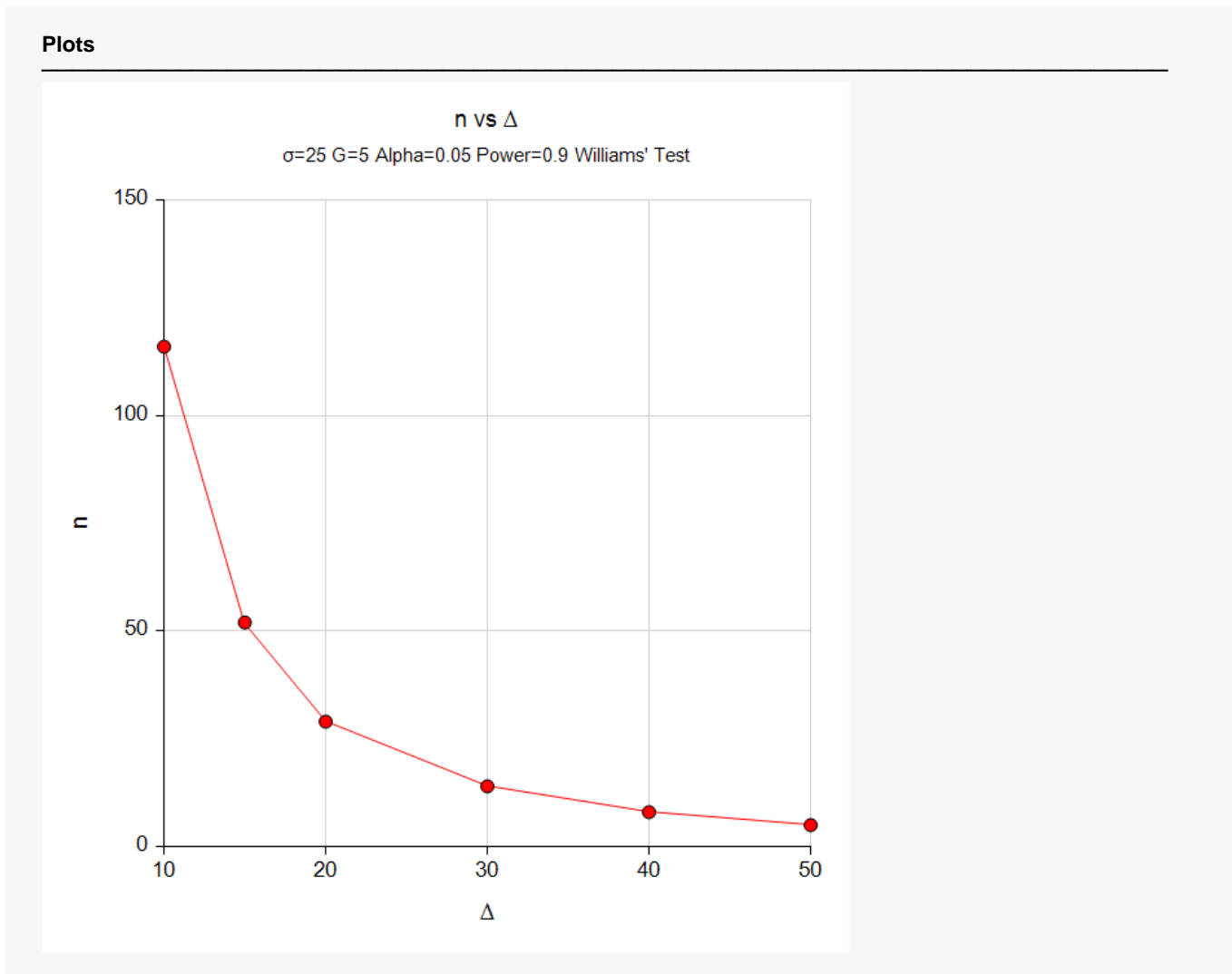
σ (sigma) is the standard deviation within each group.

Alpha

Alpha is the probability of rejecting a true null hypothesis.

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Plots Section



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

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

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
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 for Williams' Test						
Solve For:	Sample Size					
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 G	Sample Size		Minimum Detectable Difference Δ	Standard Deviation σ	Alpha
		Group n	Total N			
0.8025	4	54	216	11	22	0.05

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