**Evaluating the Dose-Response Relationship in a Clinical Trial**

# Abstract

Determining the optimal dosing of new pharmaceutical treatments is crucial for maximizing efficacy while minimizing adverse effects. Our Objective is to evaluate the dose-response relationship and the consistency of treatment effects across different sexes for a novel treatment compared with a placebo. We conducted a dose response study on clinical trial data involving 217 subjects, stratified by treatment doses (high, medium, low, and placebo). The Cochran-Mantel-Haenszel (CMH) test was employed to assess the association between dose levels and treatment response. The Breslow-Day test was employed to evaluate the homogeneity of treatment effects across sexes. The Cochran-Armitage Trend Test was employed to determine the presence of a dose-response trend. The CMH test indicated a significant positive association between increasing dose levels and treatment response. The Breslow-Day test showed no significant differences in treatment effects between sexes, suggesting homogeneity of odds ratios. Additionally, the Cochran-Armitage Trend Test confirmed a significant trend in response with increasing dose levels. The treatment exhibits a significant dose-response relationship, with higher doses leading to increased odds of a favorable response, independent of sex.

Contents

[Abstract 1](#_Toc160568443)

[1. Introduction 3](#_Toc160568444)

[2. Data Summary 3](#_Toc160568445)

[3. Methods 3](#_Toc160568446)

[4. Results 4](#_Toc160568447)

[4.1 Association Tests 4](#_Toc160568448)

[4.2 Interaction Test 5](#_Toc160568449)

[4.3 Trend Test 6](#_Toc160568450)

[5. Discussion and Conclusions 6](#_Toc160568451)

[Reference 7](#_Toc160568452)

[Appendix 7](#_Toc160568453)

# Introduction

This report presents a detailed dose-response analysis based on the data set provided at the end of this document. Dose-response analysis is an essential method in pharmacology and toxicology, offering insights into the relationship between a substance's dosage and its effect on the subjects under observation. Such analysis is critical for determining the optimal drug dosage that balances maximum efficacy with minimal side effects, a key step in developing and approving new medications.

The primary objective of this report is to explore the dose-response relationship across the varying dosage levels and to determine if there is a statistically significant trend indicating an increasing response with increasing doses. A critical part of this analysis is the implementation of a Multiple Comparison Procedure (MCP) to maintain control over the Type I error rate while conducting pairwise comparisons of each dose against the placebo. Moreover, this analysis aims to investigate the interaction effects between sex and treatment in these comparisons, employing the Breslow-Day test to examine the consistency of treatment effects across sex subgroups.

# Data Summary

The dataset presented for analysis offers a solid basis for examining the dose-response relationship within a clinical trial context. The study's design suggests it is a randomized controlled trial, characterized by several treatment levels, which facilitates a comparative analysis across different doses and a control group.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Response** | |  |  |
| **Treatment** | **1** | **0** | **Total** | **Proportion (%)** |
| 0 | 11 | 45 | 56 | 19.64 |
| 1 | 21 | 33 | 54 | 38.89 |
| 2 | 24 | 30 | 54 | 44.44 |
| 3 | 28 | 25 | 53 | 52.83 |
| **Total** | 84 | 133 | 217 | 38.71 |

Table 1. Distribution of Treatment Responses and Proportions by Dose Level

The dataset comprises four treatment levels, where Dose 0 serves as the control group, with subjects receiving a placebo. This group is essential for establishing a baseline response level and assessing the placebo effect—a phenomenon where subjects exhibit a response even without receiving an active drug component. Doses 1 through 3 represent increasing concentrations of drug, aimed at evaluating whether higher doses correspond to an increased likelihood of response. These varying doses—low, medium, and high—are intended to assess the drug's efficacy and safety across different concentrations.

The dataset's primary endpoint is the binary response variable 'resp', indicating whether a subject is a responder (resp=1) or a non-responder (resp=0). A key part of the analysis will focus on the number of responders in each treatment group. Typically, one would expect to observe a dose-dependent increase in responders, indicating a positive dose-response relationship.

# Methods

Multiple Comparison Procedures (MCP) are a collection of statistical methodologies designed to handle the challenges associated with making inferences when multiple hypotheses are being tested simultaneously. In the context of dose-response studies, or any scientific investigation involving several treatment groups, MCPs are particularly critical as they help to control for Type I error, commonly known as a "false positive.". When multiple pairwise comparisons are made, the probability of encountering at least one Type I error increases with the number of comparisons. To address this issue, MCPs adjust the significance level, thereby controlling the probability of making one or more Type I errors across the entire family of tests.

There are some well known MCPs. In this report, we use Bonferroni correction. The Bonferroni correction is a multiple comparisons correction method used in statistical hypothesis testing. It is designed to counteract the problem of Type I errors that occur when multiple pairwise tests are conducted simultaneously. In this report, we will perform multiple statistical tests on efficacy of each dose level to the placebo. In Bonferroni correction, we need to Determine the number of comparisons. In this report, we will have three comparisons when each treatment is compared to the placebo. Then, we take the desired overall alpha level () and divide it by the number of comparisons. Any individual test with a p-value below adjusted significant level () would be considered significant after the Bonferroni correction.

In this report, we use CMH test to assess the association between each dose and placebo. The Cochran-Mantel-Haenszel (CMH) test is a statistical analysis method used primarily in epidemiological studies to evaluate the association between an exposure and an outcome, while controlling for one or more confounding variables. It provides a way to test for an overall association between the exposure and the outcome across all strata.

In this report, we use the Cochran-Armitage Trend Test to assess if there is increasing dose response relationship. Developed by William G. Cochran and Peter Armitage, Cochran-Armitage Trend Test is a statistical method used primarily to analyze categorical data when the independent variable is ordinal, and the dependent variable is binary. The Cochran-Armitage Trend Test is a versatile and widely used method in the analysis of categorical data, particularly in the context of dose-response studies, allowing researchers to make more informed decisions about the efficacy and safety of treatments.

An integral part of the analysis involves exploring potential interactions between sex and treatment across each pairwise comparison. In this report, we will use the Breslow-Day test to assess the homogeneity of the odds ratios across different sex. The Breslow-Day Test, named after statisticians Norman E. Breslow and Nicholas E. Day, is a statistical test used to verify the homogeneity of the odds ratios across different strata. This test is specifically designed to assess whether the association between an exposure and an outcome is consistent across various levels of a third variable

# Results

## 4.1 Association Tests

In this report, we use CMH test to assess the association between each dose and placebo. The hypotheses for each test group are

* Null Hypothesis (): There is no difference in the odds of the outcome between the dose group and the placebo group.
* Alternative Hypothesis (): There is a difference in the odds of the outcome between the dose group and the placebo group.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Test Group** |  | **DF** |  | **OR** |
| High vs Placebo | 12.9321 | 1 | 0.0003 | 4.5818 |
| Medium vs Placebo | 7.7239 | 1 | 0.0054 | 3.2727 |
| Low vs Placebo | 4.8915 | 1 | 0.0270 | 2.6033 |

Table 2. Result of CMH test on the association between each dose and placebo

In our analysis, we conducted multiple hypothesis tests, necessitating the use of a Multiple Comparison Procedure (MCP) to avoid inflating the overall Type I error rate beyond the predetermined significance level. Using the Bonferroni correction, the significance level for each individual test is adjusted to 0.016. This adjustment ensures that the probability of making a Type I error across all tests remains at the desired significance level.

Our results indicate that for the medium and high doses, the null hypotheses can be rejected, suggesting that these doses are associated with being a responder. In contrast, the p-value for the comparison between the low dose and the placebo exceeds the adjusted significance level of 0.016. Therefore, we lack sufficient confidence to conclude an association between the low dose and responder status.

## 4.2 Interaction Test

In this report, we use the Breslow-Day test to assess the homogeneity of the odds ratios across different sex. The hypotheses for each test group are

* Null Hypothesis (): The odds ratios for the treatment effect on the outcome are homogeneous across different sexes.
* Alternative Hypothesis (): The odds ratios for the treatment effect on the outcome are not homogeneous across different sexes.

|  |  |  |  |
| --- | --- | --- | --- |
| **Test Group** |  | **DF** |  |
| High vs Placebo | 0.1919 | 1 | 0.6614 |
| Medium vs Placebo | 0.0673 | 1 | 0.7952 |
| Low vs Placebo | 0.1520 | 1 | 0.6966 |

Table 3. Result of Breslow-Day test on homogeneity of the odds ratios across different sex

When we compare different treatment levels of dose pairwise within each sex, each comparison carries the potential risk of inflating the Type I error rate. To manage this risk across multiple comparisons, employing a Multiple Comparison Procedure (MCP) is essential.

From our result, all p-values exceed the adjusted significance level. This outcome indicates that no significant interaction effects between sex and treatment dose in influencing the study outcome.

## 4.3 Trend Test

In this report, we use the Cochran-Armitage Trend Test to assess if there is increasing dose response relationship. The hypotheses for each test group are

* Null Hypothesis (): There is no trend in the response across the ordered treatment groups.
* Alternative Hypothesis (): There is a trend in the response across the ordered treatment groups.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Response** | |  |  |
| **Treatment** | **1** | **0** | **Total** | **Proportion (%)** |
| 0 | 11 | 45 | 56 | 19.64 |
| 1 | 21 | 33 | 54 | 38.89 |
| 2 | 24 | 30 | 54 | 44.44 |
| 3 | 28 | 25 | 53 | 52.83 |
| **Total** | 84 | 133 | 217 | 38.71 |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **DF** |  |  |  |
| 12.79421 | 1 | 0.0003 |  |  |
|  |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |

Table 4. Result of Cochran-Armitage Trend Test on increasing dose response relationship

From our result, p-value of trend test below the adjusted significance level. This outcome indicates that the proportion of responders increases as the dose levels increase.

# Discussion and Conclusions

The CMH test results indicate a statistically significant association between the treatment dose and the response when comparing high and medium doses to the placebo. The odds ratios suggest that higher doses are associated with higher odds of response. Specifically, the high dose has an OR of approximately 4.58 compared to the placebo. The medium dose shows a smaller but still statistically significant increase in the odds of response with ORs of approximately 3.27. However, the low dose didn’t show statistically significant increase in the odds of response after Bonferroni correction. The Breslow-Day test results for homogeneity of the odds ratios across different sexes do not show significant chi-squared values for all doses. This suggests that the odds ratios are homogeneous across the sexes, meaning that the treatment effect is consistent for both male and female subjects. Furthermore, the Cochran-Armitage trend test gives a highly significant p-value, supporting the presence of a dose-response relationship across the doses.

In summary, the statistical analyses demonstrate a significant dose-response relationship without sex-related differences in the odds of response. This result support the use of the treatment at higher doses to maximize the likelihood of a favorable outcome. However, further studies may be required to fully understand the long-term efficacy and safety profile of the treatment across a broader population and to determine the maximum beneficial dose.

# Reference

[1] Olive Jean Dunn (1961) Multiple Comparisons among Means, Journal of the American Statistical Association, 56:293, 52-64, DOI: 10.1080/01621459.1961.10482090

[2] MANTEL N, HAENSZEL W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst. 1959 Apr;22(4):719-48. PMID: 13655060.

[3] Cochran, W. G. (1954). Some Methods for Strengthening the Common χ2 Tests. Biometrics, 10(4), 417–451. https://doi.org/10.2307/3001616

[4] Breslow, N. E., N. E. Day (1980) The Analysis of Case-Control Studies Statistical Methods in Cancer Research: Vol. 1. Lyon, France, IARC Scientific Publications.

# Appendix

The R code used for this report is

1. setwd("C:/Users/Leon/Desktop/Ass2")
2. library(multcomp)
3. library(vcdExtra)
4. library(tidyverse)
5. library(DescTools)
6. library(CATT)
7. data=read.csv("DTA41.csv",header = T)
8. colnames(data)[1]="Obs"
9. data$TRT=factor(data$TRT,levels = c("0","1","2","3"),ordered = T)
10. # Fit logistic regression model
11. model <- glm(RESP ~ TRT, data = data, family = binomial)
12. # Summary of the model to check coefficients and overall fit
13. summary(model)
14. # Define contrasts for pairwise comparisons: each dose vs. placebo (TRT levels 1, 2, 3 vs. 0)
15. contrasts <- rbind("1 vs 0" = c(-1, 1, 0, 0),
16. "2 vs 0" = c(-1, 0, 1, 0),
17. "3 vs 0" = c(-1, 0, 0, 1))
19. # Apply Bonferroni correction and perform pairwise comparisons
20. summary(glht(model, linfct = mcp(TRT=contrasts), alternative = "two.sided"), test = adjusted("none"))
21. summary(glht(model, linfct = mcp(TRT = "Dunnett")))
22. data|>group\_by(TRT,RESP)|>summarise(num=n())
23. dose\_data=matrix(c(11,45,21,33,24,30,28,25),byrow = T,nrow = 4)
24. dimnames(dose\_data) <- list("trt" = c("0", "1", "2", "3"),
25. "resp" = c("Yes", "No"))
26. CochranArmitageTest(dose\_data)

The SAS code used in this report is

1. /\* Pairwise test of each dose vs placebo \*/
2. proc freq data=dta41; tables trt\*resp/cmh; where trt **in** (0,1) ;
3. proc freq data=dta41; tables trt\*resp/cmh; where trt **in** (0,2) ;
4. proc freq data=dta41; tables trt\*resp/cmh; where trt **in** (0,3) ;
6. /\* Treatment by sex interaction, using pairwise test of each dose vs placebo \*/
7. proc freq data=dta41; tables sex\*trt\*resp/cmh; where trt **in** (0,1) ;
8. proc freq data=dta41; tables sex\*trt\*resp/cmh; where trt **in** (0,2) ;
9. proc freq data=dta41; tables sex\*trt\*resp/cmh; where trt **in** (0,3) ;