# 2019 Qual - Problem 3

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*6/3/2020*

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### a) Preliminary analysis of pilot data

Table 1: Proportion of Patients who were Moderately or Severely Ill by Week for each Treatment Group

| Week | 0 | 1 | 3 | 6 |
|---|---|---|---|---|
| Placebo | 0.940 | 0.880 | 0.780 | 0.685 |
| Drug | 0.945 | 0.750 | 0.465 | 0.245 |

Table 2: Covariance Matrix of Moderate or Severe Illness by Week for Placebo Group

| Week | 0 | 1 | 3 | 6 |
|---|---|---|---|---|
| 0 | 0.057 | 0.008 | 0.022 | 0.026 |
| 1 | 0.008 | 0.106 | 0.034 | 0.052 |
| 3 | 0.022 | 0.034 | 0.172 | 0.091 |
| 6 | 0.026 | 0.052 | 0.091 | 0.217 |

Table 3: Covariance Matrix of Moderate or Severe Illness by Week for Drug Group

| Week | 0 | 1 | 3 | 6 |
|---|---|---|---|---|
| 0 | 0.052 | 0.031 | 0.011 | 0.014 |
| 1 | 0.031 | 0.188 | 0.082 | 0.057 |
| 3 | 0.011 | 0.082 | 0.250 | 0.097 |
| 6 | 0.014 | 0.057 | 0.097 | 0.186 |

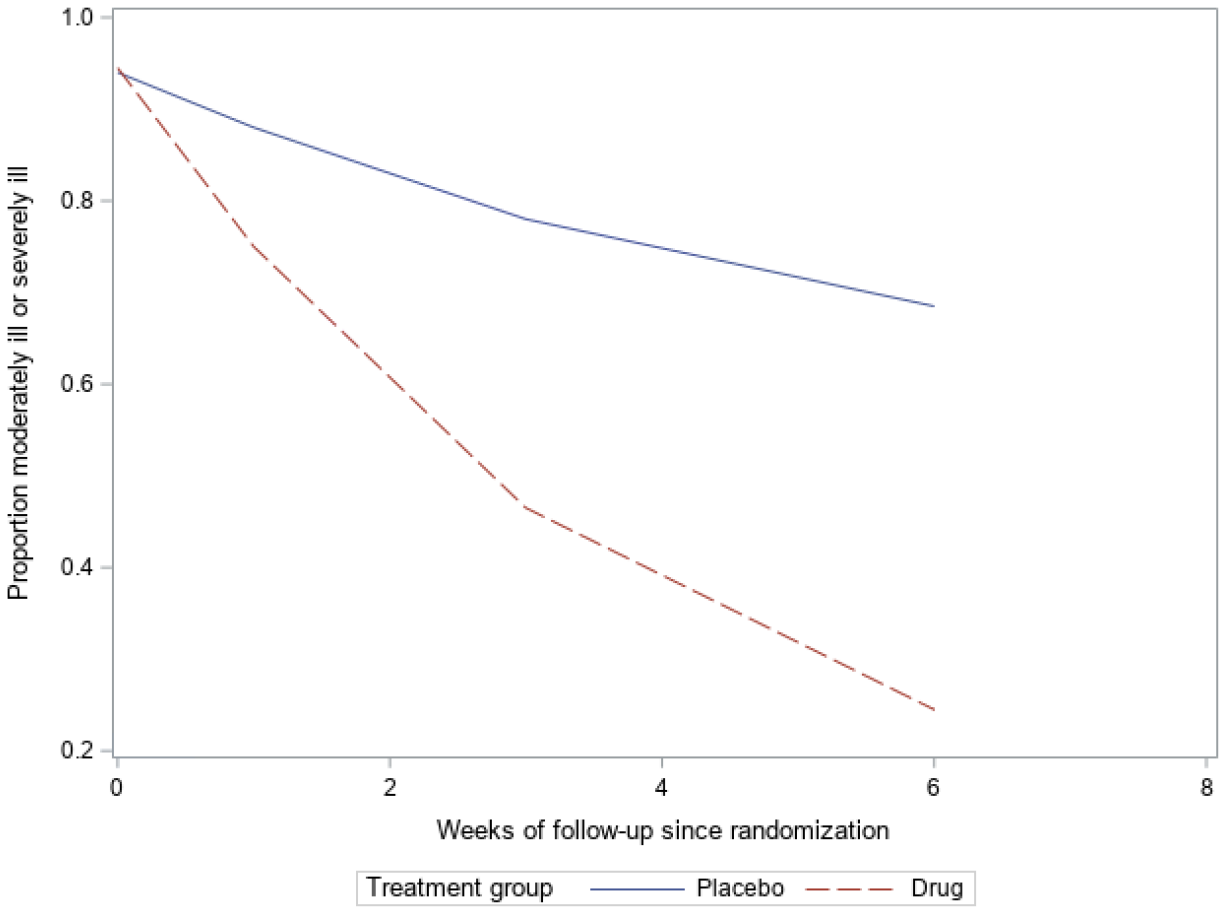


Figure 1: Proportions of Moderate or Severe Illness by Week for each Treatment Group

## b) tlc018.sas

$$\chi^2_3 = 96.7975$$

corresponds to a p-value of $< 0.001$. Therefore, we have strong evidence to reject the null hypothesis of no effect of the experimental drug compared to placebo.

## c)

$$logitE[Y_{ij}|b_{1i}] = \beta_1 + b_{1i} + \beta_2 t_{ij} + \beta_3 t_{ij} x_i$$

Table 4: Parameter Estimates and Standard Error Estimates for model M1

| Parameter | Parameter Estimate | Standard Error Estimate | 95% Confidence Interval |
|---|---|---|---|
| $\beta_1$ | 4.56 | 0.342 | (3.892, 5.235) |
| $\beta_2$ | -1.30 | 0.147 | (-1.585, -1.008) |
| $\beta_3$ | -1.41 | 0.169 | (-1.745, -1.081) |
| $\sigma^2$ | 5.15 | 0.972 | (3.241, 7.063) |

## d)

Randomized study - so at baseline there was no treatment. After baseline, there is a separate slope for drug group, so effectively there is a main effect for treatment. Therefore, justified.

## e) INTERPRETATIONS

$\beta_2$: Consider a patient $i$ in the placebo group. Let $\nu_{i0} = E[Y_{i0}|b_{1i}]$ and $\nu_{i1} = E[Y_{i1}|b_{1i}]$. Based on the model,

$$\begin{aligned} logit\nu_{i0} &= \beta_1 + b_{1i} + \beta_2(0) = \beta_1 + b_{1i} \\ logit\nu_{i1} &= \beta_1 + b_{[}1i] + \beta_2(1) \\ \Rightarrow logit\nu_{i1} - \nu_{i0} &= \beta_2 \end{aligned}$$

Thus, we see that $\beta_2$ is the difference in log odds of moderally ill or severely ill for a given patient on placebo between week 1 and baseline, conditional on this subject's specific random intercept, $b_i$. Therefore, $\hat{\beta}_2 = -1.30$, which implies that the estimated difference in log odds of moderally ill or severely ill for a given patient on placebo between week 1 and baseline, conditional on this subject's specific random intercept, $b_i$, is -1.30. Therefore, since $\hat{\beta}_2$ is negative, we have evidence that the log odds of moderate or severe onycholysis for a given patient on placebo, conditional on this subject's specific random intercept, $b_i$, is decreasing between week 1 and baseline, and indeed this was evident in the figure in part a.

$\beta_3$: Consider patient $A$ on drug and patient $B$ on placebo. Let $Y_{A1}$ be the response for patient $A$ at week 1, and let $Y_{B1}$ be the response for patient $B$ at week 1. Based on our model, we have that

$$\begin{aligned} logitE[Y_{A1}|b_{1A}] &= \beta_1 + b_{1A} + \beta_2(1) + \beta_3(1 \times 1) \\ logitE[Y_{B1}|b_{1A}] &= \beta_1 + b_{1B} + \beta_2(1) + \beta_3(1 \times 0) \\ \Rightarrow logitE[Y_{A1}|b_{1A}] - logitE[Y_{B1}|b_{1A}] &= (b_{1A} - b_{1B}) + \beta_3 \end{aligned}$$

Shown above is the contast of the log of the ratio of the two subject-specific odds of moderately ill or severely ill at week 1. Thus, it is a random subject-pair-specific log odds ratio. The expected value of the contrast is $\beta_3$, which is estimated to be -1.41, and this expectation is taken over a random pair of subject: one

being a random draw from the population of subjects on placebo and the other one being a random draw from the population of subjects on drug. The distribution of this contrast is $N(\beta_3, 2\sigma^2) = N(-1.41, 10.3)$. Based on this distribution, we can find the probability that a random subject who is on drug has a higher subject-specific risk of moderately ill or severely ill at week 1 than a random subject who is on drug

$$1 - \Phi(1.41/\sqrt{10.3}) \approx 0.33$$

This implies that the probability that a random subject who is on placebo has a higher subject-specific risk of moderately ill or severely ill at weel 1 than a random subject who is on drug is $1 - 0.33 = 0.67$, which is greater than half (0.5 would be the case in which drug is equally effective to placebo). The 5% and 95% quantiles of $N(-1.41, 10.3)$ are $(-6.69, 3.87)$, corresponding to odds ratios of 0.001 and 47.942, which is a very large range. Therefore, while we have evidence that drug is slightly more effective than placebo at reducing the subject-specific risk of moderately ill or severely ill at week 1, this pales in comparison to the heteorgeniety among patients.

$\sigma^2$: The estimate of $\sigma^2$ is $\hat{\sigma}^2 = 5.15$. Now, we assumed that $b_{1i} \sim N(0, \sigma^2)$. Therefore,

$$\begin{aligned} & 4.56 \pm 1.96\sqrt{5.15} \\ \Rightarrow & (0.1121, 9.0079) \end{aligned}$$

An interpretation to the magnitude of the estimated variance is as follows: Approximately 95% of subjects have baseline log odds of moderately ill or severely ill between 0.1121 and 9.0079.

## f)

$$logitE[Y_{ij}|b_{1i}, b_{2i}] = \beta_1 + b_{1i} + \beta_2 t_{ij} + \beta_3 t_{ij} x_i + b_{2i} t_{ij}$$

Let

$$G = \begin{bmatrix} \sigma_{11} & \sigma_{21} \\ \sigma_{21} & \sigma_{22} \end{bmatrix}$$

Table 5: Parameter Estimates and Standard Error Estimates for model M2

| Parameter | Parameter Estimate | Standard Error Estimate | 95% Confidence Interval |
|---|---|---|---|
| $\beta_1$ | 4.3829 | 0.424 | (3.549, 5.217) |
| $\beta_2$ | -1.1313 | 0.1981 | (-1.521, -0.742) |
| $\beta_3$ | -1.5629 | 0.2059 | (-1.968, -1.158) |
| $\sigma_{11}$ | 3.9854 | 1.5077 | (1.021, 6.950) |
| $\sigma_{21}$ | 0.1862 | 0.551 | (-0.897, 1.269) |
| $\sigma_{22}$ | 0.453 | 0.4645 | (-0.460, 1.366) |

## g) Seems like a bad idea since $b_{1i}$ and $b_{2i}$ are within a subject so we would expect them to have correlation and covariance?

## h) $H_0 : g_{22} = 0$ vs. $H_1 : g_{22} \neq 0$

In order to test the null hypothesis $H_0 : g_{22} = 0$ against $H_1 : g_{22} \neq 0$, which is equivalent to testing $H_0 : g_{22} = 0$ against $H_1 : g_{22} > 0$, since $g_{22}$ is a variance, I used the $-2LogL$ value from the model M2, and also fit a model like that of M2 without the random slope The $-2LogL$ value from M2 is 1339.1, and the $-2LogL$ value from the model without the random slope is 1342.7. Therefore, the likelihood ratio statistic is

$$1342.7 - 1339.1 = 3.6$$

Under the null hypothesis, this test statistic has a 50:50 mixture distribution of $\chi^2_2$ and $\chi^2_1$. In order to compute the p-value of this test statistic, we need to find the p-value from the $\chi^2_2$ distribution and the p-value from the $\chi^2_1$ distribution and take the average. The p-value from the $\chi^2_2$ distribution is 0.1653 and the p-value from the $\chi^2_1$ distribution is 0.0578. Therefore, we have the p-value for this test is 0.1112. Therefore, we do not have evidence at the $\alpha = 0.05$ level to reject the null hypothesis that $H_0 : g_{22} = 0$.

**i)**

$$logitE[Y_{ij}] = \gamma_1 + \gamma_2 t_{ij} + \gamma_3 t_{ij} x_i$$

Table 6: Parameter Estimates and Standard Error Estimates for model M3

| Parameter | Parameter Estimate | Standard Error Estimate | 95% Confidence Interval |
|---|---|---|---|
| $\gamma_1$ | 2.706 | 0.1482 | (2.416, 2.997) |
| $\gamma_2$ | -0.7976 | 0.0797 | (-0.954, -0.641) |
| $\gamma_3$ | -0.799 | 0.0869 | (-0.969, 0.629) |
| $\alpha_1$ | 1.815 | 0.4072 | (1.017, 2.613) |
| $\alpha_2$ | 1.385 | 0.4796 | (0.445, 2.325) |
| $\alpha_3$ | 2.2085 | 0.6258 | (0.982, 3.435) |
| $\alpha_4$ | 1.8225 | 0.2874 | (1.259, 2.386) |
| $\alpha_5$ | 2.4193 | 0.4166 | (1.603, 3.236) |
| $\alpha_6$ | 2.4039 | 0.309 | (1.798, 3.010) |

I used a Wald test to test the null hypothesis of no effect of the experimental drug compared to the placebo, which is equivalent to testing $H_0 : \gamma_3 = 0$. This test produced a test statistic of 84.44, which corresponds to a $\chi^2_1$ distribution, which produces a p-value of $< 0.001$. Therefore, we have strong evidence at the $\alpha = 0.05$ level to reject the null hypothesis of no effect of the experimental drug compared to the placebo.

**j) Test** $H_0 : \alpha_1 = \cdots = \alpha_6$

$W_n = 7.31$ and $p = 0.2931$