Project 1 MM924

Background

Blood pressure is the measure of the force that the heart uses to pump blood around your body [1]. This is measured in millimetres of mercury the units are mmHG [1]. There are two types of pressures systolic and diastolic, systolic pressure is the highest level of pressure that is reached when heart pushes blood out around the body and the diastolic pressure is the lowest pressure that is reached when the heart is at rest between beats [2]. This is written as 120/80 and read as '120 over 80' [2]. The top and bottom readings are the systolic and diastolic pressures [2]. The ideal pressure is between 90/60 mmHG and 120/80 mmHG [1].
High blood pressure is 140/90 mmHG or higher and Low blood pressure is 90/60 mmHG [1].
High blood pressure also known as hypertension is caused by age, race, family history, obesity or overweight, lack of exercise, smoking, eating high salt content, low potassium levels, high consumption of alcohol and pregnancy [3].
Low blood pressure also known as hypotension is caused by pregnancy, heart and heart valve condition, endocrine disorder, dehydration, blood loss, severe infection, severe allergic reaction, the lack of nutrients and medications [4].
It is given in both conditions that diet is very important either overconsumption which causes being overweight or obese causing high blood pressure and the lack of nutrient causes low blood pressure. Therefore, having a healthy balanced diet, limiting the alcohol intake, regularly exercising and stop smoking could go a long way in helping prevent both conditions [5].
If left uncheck it would cause very serious damage such as heart attack, heart disease, stroke, and kidney disease [6].
The aim of this work is to produced results of reducing blood pressure levels in obese adults by two different approaches. The first study (Study 1) is by the diet and intervention programme. Whereas the second study (Study 2) is by a medical intervention programme. We are given two data sets provided by the NHS Greater Glasgow and Clyde Health-board (A1a) (A2a).

Methods

Study 1 investigates different dietary and intervention plan to reduce the blood pressure. We have been given that the baseline blood pressure was 180mmHG. The sex of the patient was also noted. The five intervention plans were assigned were moderate exercise programme with medium salt dietary intervention (A), moderate exercise only intervention (B), no intervention (C), low salt diary intervention (D) and low salt dietary with moderate exercise intervention (E) (A1a). The blood pressure was taken six months after the patient was on one of the randomly assigned intervention plans.
We are asked to see if there is any difference in the blood pressure in the patients after six months in their intervention plans. Since sex of the patient is given, we will look at the interaction of the sex and the blood pressure of the patient. We will also use the residuals to see if the assumption of our model is valid. We will also use the Tukey's HSD to find the differences in the interventions. The analysis we will use is the two-way factorial design.
There are three hypothesis test that need to be stated, with a significance level of 0.05 we have the first hypothesis for the interaction,

$$H_0: (\alpha\beta)_{ij} = 0,$$
$$H_A: (\alpha\beta)_{ij} \neq 0, \qquad (1)$$

Where the $(\alpha\beta)_{ij}$is the interaction effect of level i of intervention plan factor and level j of the sex factor [7].
The second hypothesis is for the intervention factor,

$$H_0: \alpha_i = 0,$$
$$H_A: \alpha_i \neq 0, \qquad (2)$$

Where the α_i is the main effect of level i of intervention plan factor [7].
The third hypothesis is for the sex factor,

$$H_0: \beta_j = 0,$$
$$H_A: \beta_j \neq 0, \qquad (3)$$

Where the β_j is the main effect of level j of sex factor [7].
We will first test the interaction term if we find it not significant then we will move to the intervention factor and the sex factor separately.

Study 2 investigates if the new drug can reduce the blood pressure, twenty participants were each assigned to the three groups. The first group received the new drug (Group 1), the second group received a prescribed drug (Group 2), and the final group received no drugs (Group 3). The time was taken at their baseline, one month after and two months after. The data recorded was the participants ID number, the drug groups they were assigned to groups 1, 2 or 3, the time measurement group, and their blood pressures (A2a).
The analysis which will be used is a repeated measured design. The three drugs will be fixed and find which is better. The time measures will also be fixed, and we will find out if there is a change over time and see if there is a trend in their interactions with the drug groups. The participant of 20 patients will be nested and be the random effect [9]. We will also find the proportion of variance explained by the patient's difference.
There is a hypothesis test that need to be stated, with a significance level of 0.05, we have the first hypothesis for the interaction,

$$H_0: (\alpha\gamma)_{ik} = 0,$$
$$H_A: (\alpha\gamma)_{ik} \neq 0, \qquad (4)$$

Where the $(\alpha\gamma)_{ij}$ is the interaction effect of level i of drug factor and level k of the time factor [8].
We will also use the residuals to see if the assumption of our model is valid. This means we will have a mixed model.

Results

Descriptive statistics

In Study 1, there are 12 female observations and 13 male observations with a total of 25 observations of the sex factor. There are 5 observations in each of the 5 intervention plans (programmes). The minimum of blood pressure is 72.0 and the maximum is 181. The mean blood pressure is 121.7 and the median blood pressure is 119.0 (A1a).
Figure 1 (A1b) shows the medians are very similar in both sexes in programmes C, D and E whereas the medians of the sexes are different in programmes A and B, in fact the median are lower in the males than the females. The spread of the boxes is similar in both sexes for programmes A and D meaning there is not much variability in these plans.
There are differences in the spread of the boxes in the sexes for in programmes B, C and E, however the variability is smaller in the males than the females. In programmes B of the males there is little to no variability compared to the others.

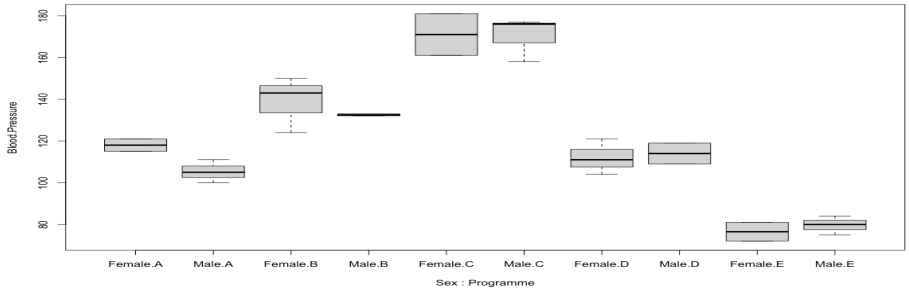

Figure 1: Boxplot of the interaction of both sex and programmes.

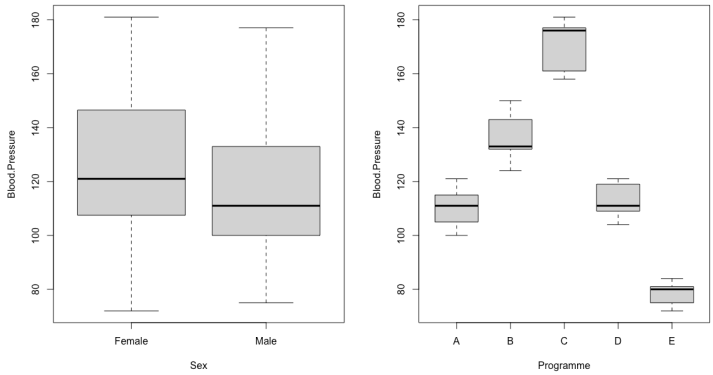

Figure 2: Boxplot of the sexes and a boxplot of the different programmes

Figure 2 (A1b) shows that the overall median of the males are lower than that of the females, the spread of the boxes are almost similar meaning the variablity of both sexes are also similar. The boxplot of the programmes that the largest median belongs to programme C and the lowest is E. The medians which are similar is A and D. The box which is the largest is programme C and the smallest box is E. Thus meaning that the largest variablity come from programme C and the lowest comes from E. Programme A,B and D have smilliar variability.

In Study 2, there are 20 participants each assigned to the three drug groups. There are 60 observations of each of the drug groups (none, old and new). There are also 60 observations of each of the time groups (baseline, one month and two months). The overall blood pressure has a minimum of 128.4 and a maximum of 142.9, the median is 140.2 and the mean is 138.2 (A2a). Figure 3 (A2b) shows that the baseline time frame and the drugs have the similar medians, and the sizes of the boxes look very similar meaning the variability is also the similar except for the “none” drug group which is slightly smaller with an outlier. The one-month time frame shows that the “none” drug has a larger median than others in the same time frame. The lowest median being the “old” drug. The spreads look the same meaning their variability is also the same with none and the “old” having outliers.
The final two-months time group we see that the “none” drug has the highest median and the smallest variability with the smallest box spread. The lowest median is from the “old” drug, this has the same size of box as the “new” group meaning a similar variability between them. The “new” drug of two-months also has an outlier.

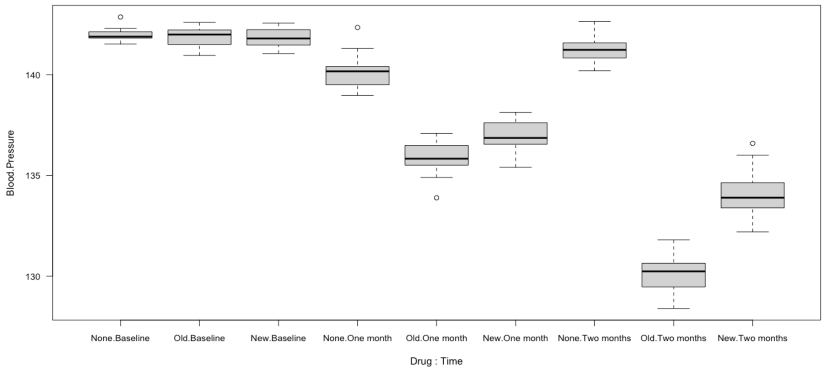

Figure 3: Two boxplots of the interaction of the drug and the time groups

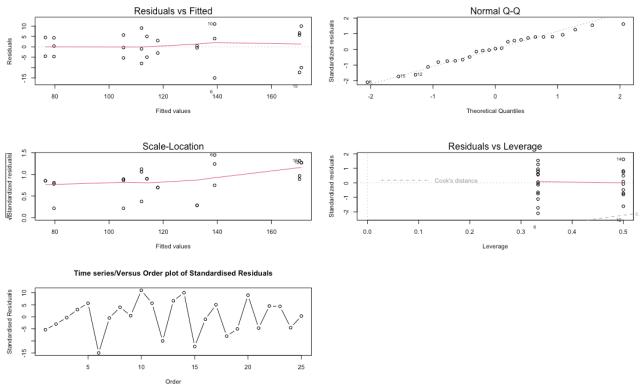

Figure 4: Five plots of Residuals vs Fitted plot, Normal QQ plot, Scale-Location plot, Residuals vs Factors levels plot and Time series/Versus Order plot of standardised Residuals.

Validating Assumptions

In Study 1, the assumptions of the model can be validated in Figure 4 (A1e). The normality of the residuals is shown by the normal QQ plot in Figure 4, the residuals would appear to be normally distributed since majority of the points lie on or close to the line. The residuals have constant variance which is shown in the three other plots in Figure 4. There is no clear pattern in the residual vs fitted plot, the scale-location plot no is clear pattern with an increase near the end of the plot. The residuals vs factor levels show no clear pattern in the given two factor levels. Since the experiment was taken in each time frame of six months, we see that using the versus order plot that there is no clear trend, and it runs in cyclic pattern therefore the residuals are independent. Overall, the assumptions are valid.

In Study 2, the assumptions of the model can be validated in Figure 5 (A2c). The normality of the residuals is shown by the normal QQ plot in Figure 5, the residuals would appear to be normally distributed since majority of the points lie on or close to the line, there is a small tailing off at each end. The residuals have constant variance which is shown in the three other plots in Figure 5. There is no clear pattern in the residual vs fitted plot except for maybe a grouping effect in the end where there seems to be more points, the scale-location plot no is clear pattern with a decrease near the end of the plot. The residuals vs factor levels show no clear pattern in the given two factor levels. Since the experiment was taken in each time frame of one and two months, we see that using the versus order plot that there is no clear trend, and it runs in cyclic pattern therefore the residuals are independent. The assumptions are also valid again.

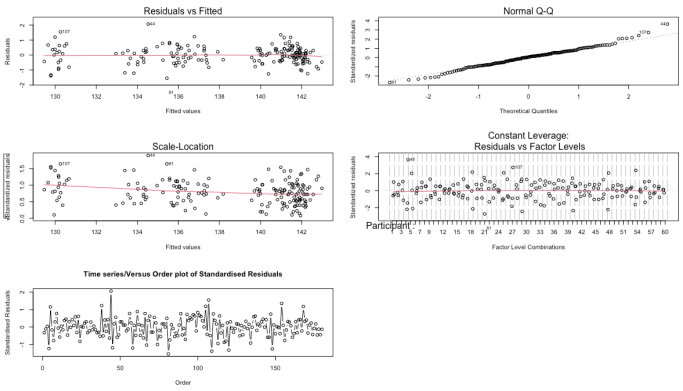

Figure 5: Five plots of Residuals vs Fitted plot, Normal QQ plot, Scale-Location plot, Residuals vs Factors levels plot and Time series/Versus Order plot of standardised Residuals.

Table 1: Unbalanced ANOVA of sex and Programme interaction

	Degrees of Freedom	Sum of Squares	Mean Sum of Square	F value	P Value
Programme	4	23409.6	5852.4	76.5354	8.543e-10
Sex	1	87.5	87.5	1.1436	0.3018
Interaction	4	209.0	52.2	0.6832	0.6144
Residuals	15	1147.0	76.5		
Total	24	24853.1			

ANOVA

In Study 1, we first use an unbalanced ANOVA table to see if there is a significance in the interaction of sex and the intervention plans. Using Table 1 (A1c) we look at the interaction and see that the p-value is greater than our significance level, therefore we cannot reject the null hypothesis (1), meaning that there is no significant difference in the interaction of sex and the programmes. This means we turn a look at our main factors separately and we also see that the sex also has a p-value larger than that of our significance level meaning we cannot reject the null hypothesis (3), therefore we have no significant difference between the sexes.
However, the programme as a very large F value and a p-value smaller than our significance level. This means we can reject the null hypothesis in favour of the alternate (3), meaning that there is significant difference between the programmes. This is also observed in Figures 1 and 2. Finally this leads us to dropping the interaction value and the sex factor as they are insignificant and proceeding on with just the programmes factor. Looking at the interaction plot in Figures 6 (A1d) we see that biggest difference is in group A but that reduces as we move to the other groups this shows the conclusion that we came across in Table 1.

In Study 2, Table 2 (A2d) shows the balanced ANOVA, we will first investigate the interaction term, we see that the F-value is very large, and the p-value is very small compared to our significance level therefore we can reject the null hypothesis in favour of the alternate (4). This means there is a significant difference within the interaction of the time and the drug groups.
Figure 7 (A2e) shows a qualitative interaction meaning that both the direction and magnitude of effects differ. The mean of the three drugs in the baselines are all the similar and are at its highest blood pressure. After one month the blood pressure decrease in all the drug groups but there a bigger rate of decrease in both the “new” and “old” drugs compared to the “none”, there is some difference in the “new” and “old” drug where the “old” drug has a lower mean blood pressure compared to the new drug. After two months the “none” drug mean blood pressure increases, this makes sense since no drug has been given to the patients. There is a bigger difference in the “new” and “old drugs”, the rate of decrease has been constant in the “old” drug leading to a lower mean compared to the “new” drug. The lowest mean measured is observed in the “old” drug after two months.

Table 2: ANOVA table with interaction term.

	Degrees of Freedom	Sum of Squares	Mean Sum of Squares	F value	p-value
Drug	2	830.5	415.2	778.9	<2e-16
Participant (Random)	57	30.4	0.5		
Time	2	1395.2	697.6	1368.8	<2e-16
Interaction	4	632.5	158.1	310.2	<2e-16
Residuals	114	58.1	0.5		
Total	179	2946.7			

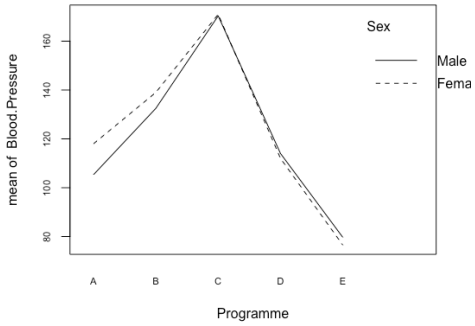

Figure 6: Interaction plot of the different programmes in different sexes.

Effects/Differences

In Study 1, we observe the means of the of the effects of programme (A1f) we see that the blood pressure of C is 170.6 which is the highest. The programme that reduced the blood pressure the most was Programme E which can be seen in Figure 6, the mean was 78.4. Programmes A and D have similar blood pressure which were at 110.4 and 112.4 meaning no big difference between them and Programme B had mean of 136.4.

Using a Tukey's HSD confidence plot (A1g) in Figure 8, we see that the differences in the mean levels of the programmes are wholly above 0 and below 0 expect for one which is Programmes A and D. meaning there is no significant difference between the two points. Therefore, the combination of moderately exercising and medium salt intake is similar to low salt intake. The pair which has the highest difference is between Programme C and E. This means having both low salt intake and moderate exercise can rapidly reduce the mean blood pressure in obese patients within six months.

Variance

In Study 2, the variance of the random variable participants is 0.007817 and the variance of the repeated observations at different time point is 0.509675. The total variability is the sum of the two variances which is 0.517492 (A2f).

The proportion of the variability associated with the participants is 1.51% whereas the proportion of variability associated with the repeated observations at different time points is 98.49%. Therefore, that the large amount of variability come from the observations at the different time intervals meaning that the study design should be revised. The nesting effect could also explain the large variability. This means there is little variability in the blood pressure of the participants.

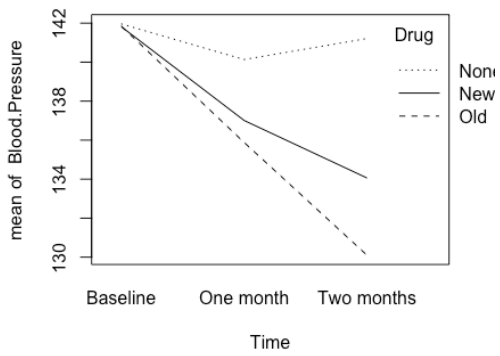

Figure 7: Interaction plot of the time and mean blood pressures in different drugs.

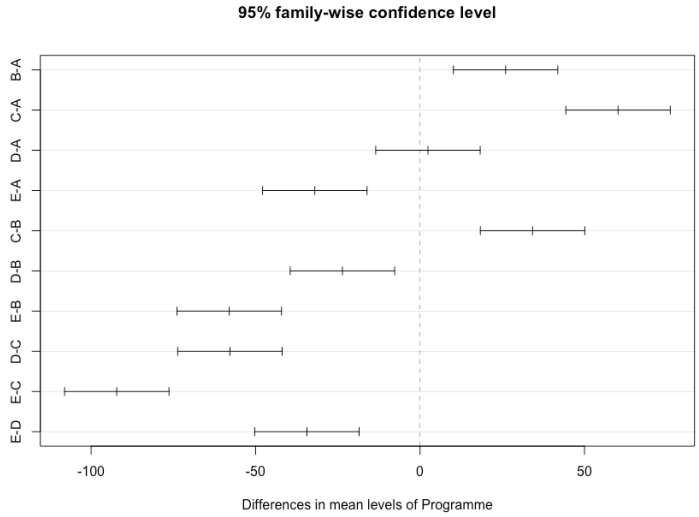

Figure 8: Tukey's HSD 95% family wise confidence interval with the differences in the means levels of the programmes

Discussion

In Study 1, the most interesting finding were that there was no interaction in the sex and programmes. Since sex contributes to many differences in biological health, but this study showed us that there were no significant differences. Programme C had no intervention plan which could be used as a reference in how much blood pressure has decreased in 6 months of the study. The most ideal blood pressure was stated to be around 90 [1] so therefore the most preferable intervention plan is plan A and D since there is no significant difference between the two programmes. Even though programme E had the lowest blood pressure at 78.4 this is would be seen as low blood pressure which could be dangerous [6].
The strength of this study was that we quickly found out that there was no significant difference in the interaction of sex and the programme which led us to drop the interaction and look at the sex and programmes separately, however the sex factor was also non-significant factor. This made us pursue the programme factor alone. The limitation of this study is we don't know how much of each programme a patient meaning how much is moderate exercise? And how much salt intake is considered as medium and low.

In Study 2, the main finding is that the no drug given to a patient would have a similar blood pressure after two months, this shows a good marker for the study as this is the placebo. The other finding is that after two months the old drug has a better effect of decreasing the blood pressure compared to the new drug. After one month there is not much difference in the old and new drug. The implications of this that after a longer duration of time the old drug is the best for the blood pressure of obese patients. It would be of some interest to see what would happen after 3 months. Does the old drug decrease the blood pressure with the same rate? Which could later cause low blood pressure [4]. The strength of this study is that the significance difference of the interaction of the drug and the time meaning we did not need to find the main effects separately. The limitations of the study were the high variability of the study design. This large variability has helped us identify where the study should focus on in creating a better design leading to a much lower variability.

Conclusion

In conclusion, the most preferable intervention plan for obese patients to reach the ideal blood pressure regardless of the sexes are moderate exercise with medium salt dietary intervention (A) and low salt dietary (D). The best drug to help obese patients decrease blood pressure is old or current prescription drug.

Reference:

[1] NHS, 12/12/2022, *What is blood pressure [Online],* https://www.nhs.uk/common-health-questions/lifestyle/what-is-blood-pressure/ Last Accessed 3/6/2023.

[2] Blood Pressure Association 2021, *What do the numbers mean?[Online],* https://www.bloodpressureuk.org/your-blood-pressure/understanding-your-blood-pressure/what-do-the-numbers-mean/ Last Accessed 3/6/2023.

[3] Mayo Clinic Staff, 15/9/2022, *High blood pressure (hypertension) [Online],* https://www.mayoclinic.org/diseases-conditions/high-blood-pressure/symptoms-causes/syc-20373410 Last Accessed 3/6/2023.

[4] Mayo Clinic Staff, 14/5/2022, *Low blood pressure (hypotension) [Online],* https://www.mayoclinic.org/diseases-conditions/low-blood-pressure/symptoms-causes/syc-20355465 Last Accessed 3/6/2023.

[5] NHS, 20/4/2023, *Prevention [Online],* https://www.nhs.uk/conditions/high-blood-pressure-hypertension/prevention/ Last Accessed 3/6/2023.

[6] CDC, 18/5/2021, *High Blood Pressure Symptoms and Causes [Online],* https://www.cdc.gov/bloodpressure/about.htm Last Accessed 3/6/2023.

[7] Robertson, C.R, 13/5/2020, *3.6: TWF Model, Assumptions, Hypotheses, Anova*, Last Accessed 3/6/2023.

[8] Robertson, C.R, 13/5/2020, *4.10: ND Interpreting Components of Variance,* Last Accessed 3/6/2023.

[9] Robertson, C.R, 13/5/2020, *4.16: RMD Lecture Example,* Last Accessed 3/6/2023.

Appendix 1:

A1a:

```
bp_intervention_data <- read.csv("BP Intervention.csv")
summary(bp_intervention_data)

#Make Factor
bp_intervention_data$Sex <- factor(bp_intervention_data$Sex)
bp_intervention_data$Programme<- factor(bp_intervention_data$Programme)
```

A1b:

```
par(mfrow =c(1,2))
boxplot(Blood.Pressure ~Sex , data = bp_intervention_data)
boxplot(Blood.Pressure ~Programme , data = bp_intervention_data)
boxplot(Blood.Pressure ~Sex:Programme , data = bp_intervention_data)
```

A1c:

```
bp_intervention_lm <- lm(Blood.Pressure ~Sex*Programme , data = bp_intervention_data)
summary(bp_intervention_lm)
anova(bp_intervention_lm)
```

A1d:

```
with(bp_intervention_data, interaction.plot(Programme, Sex,Blood.Pressure))
```

A1e:

```
par(mfrow =c(3,2))
plot(bp_intervention_lm, ask = FALSE)
plot(residuals(bp_intervention_lm),type="b",main="Time series/Versus Order plot of Standardised
Residuals",ylab="Standardised Residuals",xlab="Order")
```

A1f:

```
model.tables(bp_intervention, type = "means", se= TRUE, cterms = "Programme")
Tables of means
Grand mean

121.72

 Programme
Programme
   A     B     C     D     E
110.4 136.4 170.6 112.8  78.4

Standard errors for differences of means
       Programme
          5.306
replic.        5
```

A1g:

```
TukeyHSD(bp_intervention, which = "Programme", ordered = FALSE)
  Tukey multiple comparisons of means
    95% family-wise confidence level

Fit: aov(formula = Blood.Pressure ~ Programme, data = bp_intervention_data)

$Programme
     diff       lwr       upr     p adj
B-A  26.0   10.12292  41.877078 0.0007380
C-A  60.2   44.32292  76.077078 0.0000000
D-A   2.4  -13.47708  18.277078 0.9906813
E-A -32.0  -47.87708 -16.122922 0.0000603
C-B  34.2   18.32292  50.077078 0.0000248
D-B -23.6  -39.47708  -7.722922 0.0020516
E-B -58.0  -73.87708 -42.122922 0.0000000
D-C -57.8  -73.67708 -41.922922 0.0000000
E-C -92.2 -108.07708 -76.322922 0.0000000
E-D -34.4  -50.27708 -18.522922 0.0000229
plot(TukeyHSD(bp_intervention, which = "Programme", ordered = FALSE))
```

Appendix 2:

A2a:

```
bp_data <- read.csv("blood pressure.csv")
summary(bp_data)

#make factors

bp_data$Participant <- factor(bp_data$Participant)
bp_data$Drug <- factor(bp_data$Drug, levels = c("None", "Old", "New"))
bp_data$Time <- factor(bp_data$Time)
```

A2b:

```
boxplot(Blood.Pressure ~ Drug:Time, data = bp_data, las = 1, cex.axis= 0.9)
```

A2c:

```
#Fitting full fixed model for assumptions

bp_aov <- aov(Blood.Pressure ~ Participant+ Drug*Time, data = bp_data)
summary(bp_aov)

#Assumptions
par(mfrow =c(3,2))
plot(bp_aov, ask = FALSE)
plot(residuals(bp_aov),type="b",main="Time series/Versus Order plot of Standardised
Residuals",ylab="Standardised Residuals",xlab="Order")
```

A2d:

```
#Mixed Model
bpmix <- aov(Blood.Pressure ~  Drug*Time + Error(Participant), data = bp_data)
summary(bpmix)
```

A2e:

```
#Interaction plot
par(mfrow =c(1,1))
with(bp_data, interaction.plot(Time, Drug, Blood.Pressure))
```

A2f:

```
library(lme4)
bplmer <- lmer(Blood.Pressure ~ Drug + Time + Drug*Time + (1|Participant), data = bp_data)
summary(bplmer)

Linear mixed model fit by REML ['lmerMod']
Formula: Blood.Pressure ~ Drug + Time + Drug * Time + (1 | Participant)
   Data: bp_data

REML criterion at convergence: 399.6

Scaled residuals:
    Min      1Q  Median      3Q     Max
-2.7614 -0.5633 -0.0262  0.5490  3.5178

Random effects:
 Groups      Name        Variance Std.Dev.
 Participant (Intercept) 0.007817 0.08841
 Residual                0.509675 0.71392
Number of obs: 180, groups:  Participant, 60

Fixed effects:
                    Estimate Std. Error t value
(Intercept)          141.9605     0.1609 882.532
DrugOld               -0.1150     0.2275  -0.506
DrugNew               -0.1395     0.2275  -0.613
TimeOne month         -1.8275     0.2258  -8.095
TimeTwo months        -0.7495     0.2258  -3.320
DrugOld:TimeOne month   -4.1370     0.3193 -12.958
DrugNew:TimeOne month   -2.9845     0.3193  -9.348
DrugOld:TimeTwo months -10.9965     0.3193 -34.442
DrugNew:TimeTwo months  -7.0135     0.3193 -21.967

Correlation of Fixed Effects:
            (Intr) DrgOld DrugNw TmOnmn TmTwmn DO:TOm DN:TOm DO:TTm
DrugOld     -0.707
DrugNew     -0.707  0.500
TimeOnmonth -0.702  0.496  0.496
TimeTwmnths -0.702  0.496  0.496  0.500
DrgOld:TmOm  0.496 -0.702 -0.351 -0.707 -0.354
DrgNw:TmOnm  0.496 -0.351 -0.702 -0.707 -0.354  0.500
DrgOld:TmTm  0.496 -0.702 -0.351 -0.354 -0.707  0.500  0.250
DrgNw:TmTwm  0.496 -0.351 -0.702 -0.354 -0.707  0.250  0.500  0.500
```