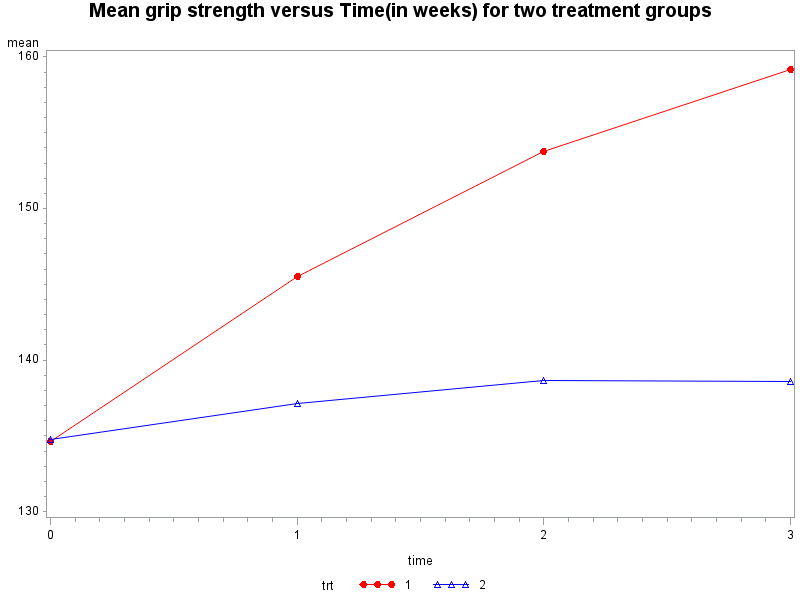
1. **Obtain the sample size, and the sample means and standard deviations of the grip strengths at each occasion for each treatment group. On the same graph, plot the mean grip strength versus time (in weeks) for each of the two treatment groups. Describe the general characteristics of the time trends for the two groups.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Treatment | time | Sample Size | mean | std |
| 1 | 0 | 26 | 134.615 | 71.2938 |
| 1 | 1 | 26 | 145.500 | 68.9401 |
| 1 | 2 | 26 | 153.769 | 70.9356 |
| 1 | 3 | 26 | 159.154 | 71.4124 |
| 2 | 0 | 32 | 134.750 | 72.7071 |
| 2 | 1 | 32 | 137.125 | 75.0315 |
| 2 | 2 | 32 | 138.625 | 71.4480 |
| 2 | 3 | 32 | 138.594 | 73.5540 |



Describe the trend:

The mean response value at the baseline for the two treatment groups are almost the same (134.615 versus 134.750) which makes sense since this is a randomized clinical trial. After baseline, treatment group 1 shows a noticeable increase trend, while treatment 2 shows a slight increase at time 1 and then almost flat.

1. **With baseline (month 0) and the treatment A as the reference group, write out the complete definition of the regression model for the analysis of response profiles for mean grip strength. In this model, let β denote the vector of parameters in the model for the means and assume an unstructured variance-covariance structure.**

Let for all patient at all occasions

Creating indicator variables for treatment group and time:

Treatment:

Let if patient randomized to treatment 1, to treatment 2

Time:

Let if measurement at week 3, otherwise

Let if measurement at week 2, otherwise

Let if measurement at week 1, otherwise

Analysis of response profiles model can be expressed as:

Or equivalently, the conditional mean can be expressed as:

And assume an unstructured variance-covariance matrix for the repeated measures for the same patient.

1. **Using PROC MIXED, fit the model described in question 2. Include the SOLUTION (or S) option on the MODEL statement to obtain estimates and standard errors for the components of β. Include the CHISQ option on the MODEL statement and hence evaluate whether there is evidence of a difference in the pattern of change over time in mean grip strength between the two treatment groups. Justify your answer.**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Solution for Fixed Effects | | | | | | | |
| Effect | **trt** | **time** | **Estimate** | **Standard Error** | **DF** | **t Value** | **Pr > |t|** |
| Intercept |  |  | 134.62 | 14.1360 | 56 | 9.52 | <.0001 |
| trt | **2** |  | 0.1346 | 19.0311 | 56 | 0.01 | 0.9944 |
| time |  | **3** | 24.5385 | 3.9255 | 56 | 6.25 | <.0001 |
| time |  | **2** | 19.1538 | 3.4572 | 56 | 5.54 | <.0001 |
| time |  | **1** | 10.8846 | 3.0531 | 56 | 3.57 | 0.0008 |
| trt\*time | **2** | **3** | -20.6947 | 5.2849 | 56 | -3.92 | 0.0002 |
| trt\*time | **2** | **2** | -15.2788 | 4.6545 | 56 | -3.28 | 0.0018 |
| trt\*time | **2** | **1** | -8.5096 | 4.1104 | 56 | -2.07 | 0.0430 |

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Type 3 Tests of Fixed Effects | | | | | | |
| Effect | **Num DF** | **Den DF** | **Chi-Square** | **F Value** | **Pr > ChiSq** | **Pr > F** |
| trt | 1 | 56 | 0.34 | 0.34 | 0.5596 | 0.5620 |
| time | 3 | 56 | 30.76 | 10.25 | <.0001 | <.0001 |
| trt\*time | 3 | 56 | 15.58 | 5.19 | 0.0014 | 0.0031 |

The question of main scientific interest concerns the comparison of the two treatment groups in terms of their patterns of change from baseline in the mean grip strength. This question translates directly into the test of trt\*time interaction term. The test of trt\*time interaction yields a Wald statistic of 15.58 with 3 degrees of freedom. When compared with the reference chi-squared distribution with 3 degrees of freedom, p-value=0.0014, there is a strong evidence to reject the null hypothesis and conclude that the patterns of change from baseline are not the same in the two groups. But the multivariate Wald test is an omnibus test, it doesn’t tell us how do the patterns differentiate from each other.

1. **Provide an interpretation for the estimate of each component of β.**

The mean grip strength for treatment 1 is:

The mean grip strength for treatment 2 is:

is the mean grip strength for patients in treatment 1 at baseline. The estimate indicates that, the mean grip strength for patients in treatment 1 at baseline is 134.62 (<.0001).

is the difference of mean response between treatment 2 and treatment 1, at baseline. The estimate indicates that, the difference of mean grip strength between the two groups is 0.1346 (p=0.9944), that is, the baseline responses for the two groups are not significantly different, this corresponds to the randomized design, hence we can exclude the main effect of treatment from the model.

,, and are the change of mean response from baseline (Week 0) in Week 3, Week 2, and Week 1 for patients in treatment group 1, respectively. The estimates indicate that there are significant changes of mean grip strength from baseline for patients in treatment 1 at all follow-up occasions. More precisely, 10.8846 (0.0008) increase in the mean at week 1 from baseline, 19.1538(<.0001) increase at week 2 from baseline, and 24.5385 (<.0001) increase in the mean at week 3 from baseline.

,, and are the differences of treatment 2 versus treatment 1 in the change of mean response from baseline in Week 3, Week 2, and Week 1, respectively. The estimates indicate that treatment 2 has lower change of mean response from baseline in all follow-up occasions; more precisely, at week 1, the change of mean grip strength from baseline for patients in treatment 2 is 8.5096 (p=0.043<0.05) smaller than that of treatment 1, at week 2, the change of mean grip strength from baseline for patients in treatment 2 is 15.2788 (p=0.0018<0.05) smaller than that of treatment 1, and at week 3, the change of mean grip strength from baseline for patients in treatment 2 is 20.6947 (p=0.0002<0.05) smaller than that of treatment 1.

1. **Show how the estimates for the components of β can be used to construct the sample means at each measurement time in each treatment group. Compare these estimated means with the sample means that you obtained in question 1. Do they differ? If so, can you suggest why?**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Baseline (Week 0) | Week 1 | Week 2 | Week 3 |
| Treatment 1 |  |  |  |  |
| Treatment 1 |  | + | + |  |

Model Estimation:

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Baseline (Week 0) | Week 1 | Week 2 | Week 3 |
| Treatment 1 | 134.62 | 145.5046 | 153.7738 | 159.1585 |
| Treatment 1 | 134.7546 | 137.1296 | 138.6296 | 138.5984 |

Sample means:

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Baseline (Week 0) | Week 1 | Week 2 | Week 3 |
| Treatment 1 | 134.615 | 145.500 | 153.769 | 159.154 |
| Treatment 1 | 134.750 | 137.125 | 138.625 | 138.594 |

They differ after the second decimal point. In theory, the saturated model should have the exactly same mean as the sample mean, at each measurement time in each treatment group. But different procedures in SAS may have different degree of precision or rounding, that makes the model estimated means from PROC MIXED slightly different from the sample means from PROC MEANS, in the sense that they only differ after the second decimal point.

1. **Now conduct a profile analysis (week, treatment, week\*treatment) on the difference vector D = (Y1-Y0, Y2-Y0, Y3-Y0). Show that this analysis yields the same conclusions as those obtained from the full profile analysis fit in question 3.**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Solution for Fixed Effects | | | | | | | |
| Effect | **trt** | **time** | **Estimate** | **Standard Error** | **DF** | **t Value** | **Pr > |t|** |
| Intercept |  |  | 10.8846 | 3.0531 | 56 | 3.57 | 0.0008 |
| trt | **2** |  | -8.5096 | 4.1104 | 56 | -2.07 | 0.0430 |
| time |  | **3** | 13.6538 | 3.6410 | 56 | 3.75 | 0.0004 |
| time |  | **2** | 8.2692 | 3.0088 | 56 | 2.75 | 0.0080 |
| trt\*time | **2** | **3** | -12.1851 | 4.9018 | 56 | -2.49 | 0.0159 |
| trt\*time | **2** | **2** | -6.7692 | 4.0507 | 56 | -1.67 | 0.1003 |

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Type 3 Tests of Fixed Effects | | | | | | |
| Effect | **Num DF** | **Den DF** | **Chi-Square** | **F Value** | **Pr > ChiSq** | **Pr > F** |
| trt | 1 | 56 | 13.50 | 13.50 | 0.0002 | 0.0005 |
| time | 2 | 56 | 9.63 | 4.81 | 0.0081 | 0.0118 |
| trt\*time | 2 | 56 | 6.19 | 3.10 | 0.0452 | 0.0530 |

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Contrasts | | | | | | |
| Label | **Num DF** | **Den DF** | **Chi-Square** | **F Value** | **Pr > ChiSq** | **Pr > F** |
| Joint test of trt and trt\*time | 3 | 56 | 15.58 | 5.19 | 0.0014 | 0.0031 |

The change score in the mean grip strength for treatment 1 is:

The change score in the mean grip strength for treatment 2 is:

Because the outcome is a change score (the change from baseline), this approach alters the interpretation of the tests for all effects. The test for trt\*time interaction becomes a test for parallel profiles for the changes from baseline in the mean response on time 2 and 3; the test for the main effect of treatment becomes a test that the changes from baseline at time 1 are the same for two treatment groups. Thus, to address the main question of interest of whether patterns of change over time are the same in the two treatment groups, the test of interest is a 3 degrees of freedom joint test of the main effect of treatment and the trt\*time interaction. The 3 d.f. Wald statistic is 15.58 (p=0.0014), thus it’s exactly the same result as question 3, and conclude that there is significant difference in the patterns of change from baseline are not the same in the two groups.

1. **Run an ANCOVA analysis of the outcomes (Y1, Y2, Y3), including the effects of week, treatment, and week \* treatment as well as each subject’s baseline measurement as covariates. Compare both the week, treatment, and week \* treatment effect estimates and standard errors to those from the profile analysis results from Q3. Explain why these results are the same or different from this earlier analysis.**

**ANCOVA**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Solution for Fixed Effects | | | | | | | |
| Effect | **trt** | **time** | **Estimate** | **Standard Error** | **DF** | **t Value** | **Pr > |t|** |
| Intercept |  |  | 14.4703 | 4.7419 | 55 | 3.05 | 0.0035 |
| Y0 |  |  | 0.9734 | 0.02687 | 55 | 36.22 | <.0001 |
| trt | **2** |  | -8.5060 | 4.1282 | 55 | -2.06 | 0.0441 |
| time |  | **3** | 13.6538 | 3.6409 | 55 | 3.75 | 0.0004 |
| time |  | **2** | 8.2692 | 3.0088 | 55 | 2.75 | 0.0081 |
| trt\*time | **2** | **3** | -12.1851 | 4.9017 | 55 | -2.49 | 0.0160 |
| trt\*time | **2** | **2** | -6.7692 | 4.0507 | 55 | -1.67 | 0.1004 |

**profile analysis**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Solution for Fixed Effects | | | | | | | |
| Effect | **trt** | **time** | **Estimate** | **Standard Error** | **DF** | **t Value** | **Pr > |t|** |
| Intercept |  |  | 134.62 | 14.1360 | 56 | 9.52 | <.0001 |
| trt | **2** |  | 0.1346 | 19.0311 | 56 | 0.01 | 0.9944 |
| time |  | **3** | 24.5385 | 3.9255 | 56 | 6.25 | <.0001 |
| time |  | **2** | 19.1538 | 3.4572 | 56 | 5.54 | <.0001 |
| time |  | **1** | 10.8846 | 3.0531 | 56 | 3.57 | 0.0008 |
| trt\*time | **2** | **3** | -20.6947 | 5.2849 | 56 | -3.92 | 0.0002 |
| trt\*time | **2** | **2** | -15.2788 | 4.6545 | 56 | -3.28 | 0.0018 |
| trt\*time | **2** | **1** | -8.5096 | 4.1104 | 56 | -2.07 | 0.0430 |

In ANCOVA, the main effect of treatment is the difference of mean response in week 1(reference group of week) compare treatment 2 to treatment 1, it’s corresponding to the trt\*time interaction at week 1. Thus, their effect estimation are the same (both are -8.5). ANCOVA has smaller standard errors.

In ANCOVA, the main effect of time is the change of mean responses in treatment 1(reference group of trt) from week 1 at week 2 (8.27) and 3(13.65), they corresponds to the main effect of time 2 and 3 minus the main effect of time 1 in profile analysis, which yield to 8.27 and 13.65 as well. Thus, their effect estimation are the same; ANCOVA has smaller standard errors. ANCOVA has smaller standard errors.

In ANCOVA, the effect of trt\*time interaction is the difference in the change from week 1 for the two groups at week 2(-6.8) and week 3(-12.2), they corresponds to the interaction effect of time 2 and 3 minus the interaction effect of time 1, which yield to -6.8 and -12.2 as well. Thus, their effect estimations are the same. ANCOVA has smaller standard errors.

In summary, in randomized trial, ANCOVA is more preferred. The mean response at baseline is independent of treatment assignment, once incorporated in the right side of the regression equation, it will reduce the standard errors of the parameter estimations, that is, ANCOVA approach yields estimates of treatment effects the same as standard profile analysis but with smaller standard errors, or greater efficiency.

\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*

Appendix: SAS Code

\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*;

\*import dataset;

**data** Grip;

infile 'C:\data\Projects\APCD High Cost\Longitudinal\compgrip.txt';

input id trt Y0 Y1 Y2 Y3;

**run**;

\*Univariate format;

**data** grip\_l;

set grip;

y=y0;time=**0**;output;

y=y1;time=**1**;output;

y=y2;time=**2**;output;

y=y3;time=**3**;output;

drop y0 y1 y2 y3;

**run**;

/\*

Q1:Obtain the sample size, and the sample means and standard deviations of the

grip strengths at each occasion for each treatment group.

\*/**proc** **sort** data=grip\_l;by trt time;**run**;

**proc** **means** data=grip\_l noprint;

by trt time;

var y;

output out=meangrip n=n mean=mean std=std;

**proc** **print** data=meangrip;var trt time n mean std;

**run**;

\*plot the mean grip strength versus time (in weeks) for each of the two treatment groups;

**proc** **gplot** dat=meangrip ;

title "Mean grip strength versus Time(in weeks) for two treatment groups";

symbol1 color=red interpol=join value=dot;

symbol2 color=blue interpol=join value=triangle;

plot mean\*time=trt;

**run**;

\*Q3: PROC MIXED for profile analysis;

**proc** **sort** data=grip\_l;by descending trt descending time;**run**;

**proc** **mixed** data=grip\_l order=data;

class id trt time;

model y=trt time trt\*time/solution chisq;

repeated time /type=un subject=id r rcorr;

**run**;

\*Q6: PROC MIXED for profile analysis on the difference vector;

**data** grip\_diff;

set grip;

y=y1-y0;time=**1**;output;

y=y2-y0;time=**2**;output;

y=y3-y0;time=**3**;output;

drop y0 y1 y2 y3;

**run**;

**proc** **sort** data=grip\_diff;by descending trt descending time;**run**;

**proc** **mixed** data=grip\_diff order=data;

class id trt time;

model y=trt time trt\*time/solution chisq ;

repeated time /type=un subject=id r rcorr;

contrast "Joint test of trt and trt\*time" trt **1** -**1** trt\*time **1** **0** **0** -**1** **0** **0** ,

trt **1** -**1** trt\*time **0** **1** **0** **0** -**1** **0**, trt **1** -**1** trt\*time **0** **0** **1** **0** **0** -**1** /chisq;

**run**;\* constrast: think two means to be the same, not which beta's to be zero;

\*Q7: ANCOVA;

**data** grip\_ancova;

set grip;

y=y1;time=**1**;output;

y=y2;time=**2**;output;

y=y3;time=**3**;output;

drop y1 y2 y3;

**run**;

**proc** **sort** data=grip\_ancova;by descending trt descending time;**run**;

**proc** **mixed** data=grip\_ancova order=data;

class id trt time;

model y=y0 trt time trt\*time/solution chisq;

repeated time /type=un subject=id r rcorr;

**run**;