STAT 36900: Homework 1

Robert Winter

Table of Contents

1 Introduction

The data for this problem are from a study investigating treatment-related changes in symptomatology severity in a sample of schizophrenic patients. Subjects were assigned to one of four treatments: placebo, chlorpromazine, fluphenasinze, and thioridazine; however, for this problem the three non-placebo drug groups have been combined into one group. Severity of schizophrenic symptomatology was assessed across time using the Inpatient Multidimensional Psychiatric Scale (IMPS) Item 79, "Severity of Illness," which was coded as: 1=normal, not at all ill; 2=borderline mentally ill, 3=mildly ill, 4=moderately ill, 5=markedly ill, 6=severely ill, or 7=among the most extremely ill. Patients were sometimes classified by two psychiatric raters (in terms of the severity as measured by this scale) and when these rates differed an average of the two scores was used for that patient at that timepoint. The file `SCHIZREP.DAT.TXT` contains some of the data from this study. Specifically, in this file you'll find 1603 records from 437 patients with five fields of data:

- **field 1: Patient ID**
- **field 2: IMPS79 (7-point measure of severity of illness)**
- **field 3: Week, from 0 (baseline) to Week 6 (most measurements were on Weeks 0, 1, 3, and 6)**
- **field 4: treatment group (0=placebo, 1=drug)**
- **field 5: sex (0=female, 1=male)** ***ignore this variable***

2 Question 1

Obtain the IMPS79 means, standard deviations, and sample sizes across the 7 timepoints. Comment on the values you obtain and what might be suggested for a statistical modeling of these data (ideas about time-related trends might help here).

```
. infile PatientID IMPS79 Week treatment sex ///
> using SCHIZREP.DAT.txt, clear
(1,603 observations read)
. tabulate Week, summarize(IMPS79) wrap
```

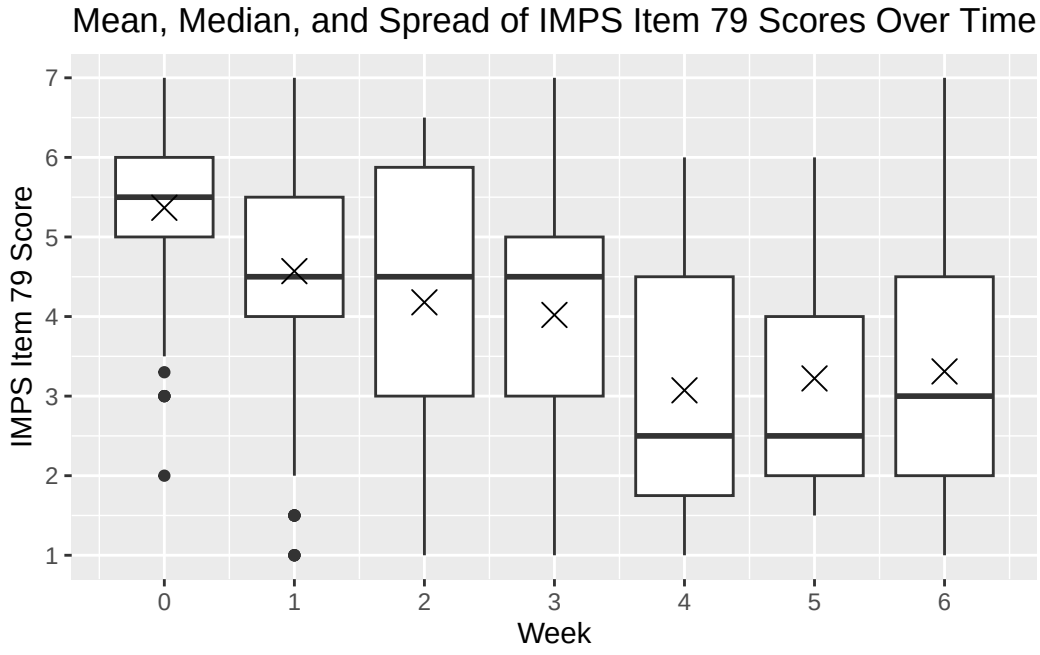
Week	Summary of IMPS79 Mean	Std. dev.	Freq.
0	5.3668203	.86678804	434
1	4.5706573	1.22868	426
2	4.1785714	1.8251148	14
3	4.0200535	1.4372296	374
4	3.0727273	1.6965205	11
5	3.2222222	1.7159384	9
6	3.3101493	1.4828213	335
Total	4.3730505	1.4714927	1,603

We observe that from Weeks 0 through 4, the average IMPS79 score steadily declines (i.e., illness is scored as less severe), but in Weeks 5 and 6, the average IMPS79 score actually begins to slowly increase again. This decreasing-to-increasing pattern suggests that a quadratic trend across timepoints may be appropriate for modeling IMPS79 scores. It is also worth pointing out that some timepoints have very few observations, with less than 15 observations recorded for each of Weeks 2, 4, and 5 (whereas the rest of the weeks have anywhere from 335 to 434 observations each). So, it is possible that sampling bias during these weeks has obscured the true trend in IMPS79 scores over the course of the study. For example, if disproportionately many of the nine patients observed during Week 5 happened to be assigned

to the placebo, it would not be surprising that the average score this week was higher. It is therefore important to further investigate whether there really is a quadratic trend in the data, or if this apparent trend is really just a consequence of having small samples in Weeks 4 and 5.

Moreover, the standard deviation in IMPS79 scores increases significantly from 0.867 during Week 0 to 1.229 during Week 1, and then fluctuates around this higher level (as low as 1.437 and as high as 1.825) from Weeks 2 through 6. This pattern makes sense: at the beginning of the study, all of the participants have untreated schizophrenia, so would all be expected to score near one another. Starting in Week 1, however, participants in the three treatment groups have taken a drug while participants in the control group have only taken a placebo. If the drugs actually have an effect on schizophrenic symptoms, we would expect the scores for the treated patients to fall while the scores of the patients taking the placebo might not, widening the spread of scores. By Week 2, with more time for the drugs to take effect in the treated participants, we observe an even greater spread of scores.

These general patterns of central tendency and spread can also be seen in the boxplot below (though depicting the median and 1.5x the IQR rather than the mean and standard deviation). We also plot the means for each week using a $\times$ symbol.



3 Question 2

For this question ignore treatment group, and just fit random-effects model(s) for the trend in IMPS79 scores across time. Using IMPS79 as your dependent variable, examine whether the overall trend across timepoints is linear or

quadratic. Regarding the random effects, is there significant individual-level variation in the trends across time; specifically, is there significant individual-level variation in first, the linear, and then, the quadratic trend? Write down both the within-subjects and between-subjects components of your final model. Describe the meaning of the various model parameters and your conclusions regarding their statistical significance.

3.1 Exploration: Linear Time Trend

First, we consider a linear time-trend model with random intercepts and random trends, allowing the linear trend in IMPS Item 79 score over time to vary by individual.

```
. infile PatientID IMPS79 Week treatment sex ///
> using SCHIZREP.DAT.txt, clear
(1,603 observations read)
.
. * Random intercept and linear time trend
. mixed IMPS79 Week || PatientID: Week, covariance(unstructured) mle

Performing EM optimization ...

Performing gradient-based optimization:
Iteration 0:  Log likelihood =  -2437.423
Iteration 1:  Log likelihood = -2437.0953
Iteration 2:  Log likelihood = -2437.0949
Iteration 3:  Log likelihood = -2437.0949

Computing standard errors ...

Mixed-effects ML regression                     Number of obs    =  1,603
Group variable: PatientID                       Number of groups =    437
                                                Obs per group:
                                                              min =      2
                                                              avg =    3.7
                                                              max =      5
                                                Wald chi2(1)     = 541.02
Log likelihood = -2437.0949                     Prob > chi2      = 0.0000

------------------------------------------------------------------------------
      IMPS79 | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
        Week |  -.3300519   .0141897   -23.26   0.000    -.3578633   -.3022406
       _cons |   5.125357   .0436605   117.39   0.000     5.039784     5.21093
------------------------------------------------------------------------------
```

```
------------------------------------------------------------------------------
  Random-effects parameters  |   Estimate   Std. err.      [95% conf. interval]
-----------------------------+------------------------------------------------
PatientID: Unstructured      |
                   var(Week) |   .0401466   .0063813      .0294003    .0548209
                  var(_cons) |   .4325652   .0594326      .3304457    .5662432
             cov(Week,_cons) |   .0374085   .0138102      .0103409     .064476
-----------------------------+------------------------------------------------
               var(Residual) |   .6990585   .0362713      .6314633    .7738894
------------------------------------------------------------------------------
LR test vs. linear model: chi2(3) = 472.07                Prob > chi2 = 0.0000

Note: LR test is conservative and provided only for reference.
```

Note that the point estimate on the `Week` variable is statistically significant, indicating that there is a negative linear trend in IMPS Item 79 score over time at the population level.

To determine whether there is also individual-level heterogeneity in the linear trend of IMPS Item 79 scores over time, we compare the above model against a model with random intercepts, but not random time trends.

```
. infile PatientID IMPS79 Week treatment sex ///
> using SCHIZREP.DAT.txt, clear
(1,603 observations read)
.
. * Random intercept
. mixed IMPS79 Week || PatientID: , covariance(unstructured) mle
note: single-variable random-effects specification in PatientID equation;
      covariance structure set to identity.

Performing EM optimization ...

Performing gradient-based optimization:
Iteration 0:  Log likelihood = -2512.7192
Iteration 1:  Log likelihood = -2512.7192

Computing standard errors ...

Mixed-effects ML regression                     Number of obs    =  1,603
Group variable: PatientID                       Number of groups =    437
                                                Obs per group:
                                                              min =      2
                                                              avg =    3.7
                                                              max =      5
```

```
                                                Wald chi2(1)     =  844.81
Log likelihood = -2512.7192                     Prob > chi2      =  0.0000

------------------------------------------------------------------------------
      IMPS79 | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
        Week |  -.3244892    .011164   -29.07   0.000    -.3463702   -.3026081
       _cons |   5.119027   .0531587    96.30   0.000     5.014838    5.223217
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects parameters  |   Estimate   Std. err.     [95% conf. interval]
-----------------------------+------------------------------------------------
PatientID: Identity          |
                  var(_cons) |    .699818   .0659655      .5817683    .8418218
-----------------------------+------------------------------------------------
               var(Residual) |   .9433866   .0390265      .8699149    1.023064
------------------------------------------------------------------------------
LR test vs. linear model: chibar2(01) = 320.82        Prob >= chibar2 = 0.0000
```

As seen above, the random intercept model has a log likelihood of -2512.7192, and the random intercept and trend model has a log likelihood of -2437.0949, so the likelihood ratio χ^2 statistic is $\text{LR}\,\chi^2 \approx -2 \times (-2512.7192 - (-2437.0949)) = 151.2486$. Since we are testing the null hypothesis $H_0 : \sigma^2_{\upsilon_1} = \sigma_{\upsilon_0\upsilon_1} = 0$, we test the significance of this χ^2 statistic using the chi-bar-squared test with one and two degrees of freedom:

```
. display(0.5*chi2tail(1, 151.2486) + 0.5*chi2tail(2, 151.2486))
7.636e-34
```

Since $p = 7.636 \times 10^{-34} < 0.001$, there is statistically significant heterogeneity in participants' linear trends of IMPS79 score over time. In fact, a 95% plausible value interval for participants' linear time trends is approximately $(-0.330 - 1.96\sqrt{0.040}, -0.330 + 1.96\sqrt{0.040}) = (-0.722, 0.062)$. That the right endpoint of this interval is positive means that some participants' scores are actually worsening over time!

It is also noteworthy that in a likelihood ratio test against a linear model, our random intercept model above has a statistically significant χ^2 statistic, indicating that there is heterogeneity in participants' IMPS Item 79 scores at the beginning (i.e., Week 0) of the study.

3.2 Exploration: Quadratic Time Trend

Now, we consider models that allow for quadratic changes in IMPS Item 79 score over time. In particular, we begin by augmenting the previous model to include a population-

wide quadratic change in IMPS79 scores over time (but not yet including individual-level heterogeneity in that quadratic change).

```
. infile PatientID IMPS79 Week treatment sex ///
> using SCHIZREP.DAT.txt, clear
(1,603 observations read)
.
. generate Week2 = Week*Week
.
. * Quadratic effect of week -- population-level only
. mixed IMPS79 Week Week2 || PatientID: Week, covariance(unstructured) mle

Performing EM optimization ...

Performing gradient-based optimization:
Iteration 0:  Log likelihood = -2409.0378
Iteration 1:  Log likelihood = -2408.8416
Iteration 2:  Log likelihood = -2408.8416

Computing standard errors ...

Mixed-effects ML regression                     Number of obs    =  1,603
Group variable: PatientID                       Number of groups =    437
                                                Obs per group:
                                                              min =      2
                                                              avg =    3.7
                                                              max =      5
                                                Wald chi2(2)     = 605.65
Log likelihood = -2408.8416                     Prob > chi2      = 0.0000

------------------------------------------------------------------------------
      IMPS79 | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
        Week |  -.5819307   .0358414   -16.24   0.000    -.6521784   -.5116829
       Week2 |   .0424845   .0055663     7.63   0.000     .0315748    .0533942
       _cons |   5.274477   .0477457   110.47   0.000     5.180897    5.368057
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects parameters  |   Estimate   Std. err.     [95% conf. interval]
-----------------------------+------------------------------------------------
PatientID: Unstructured      |
                   var(Week) |   .0418409   .0062828      .0311734    .0561588
                  var(_cons) |   .4555111   .0588784      .3535693    .5868451
             cov(Week,_cons) |   .0331246   .0136197      .0064304    .0598188
```

```
------------------------------+------------------------------------------------
               var(Residual) |   .6538218   .0339305      .5905895    .7238241
------------------------------------------------------------------------------
LR test vs. linear model: chi2(3) = 501.04                Prob > chi2 = 0.0000

Note: LR test is conservative and provided only for reference.
```

Note that the point estimates on the `Week` and `Week2` (i.e., $Week^2$) variables are both statistically significant, indicating that at the population level, (1) IMPS Item 79 scores decline over time, but (2) the rate of this decline is decelerating over time. Since this model only differs from our previous model by the addition of the `Week2` variable, we can conclude that there is a statistically significant population-level quadratic trend in IMPS Item 79 scores over time.

To determine whether there is also individual-level heterogeneity in this quadratic trend, we compare the above model against a model with random intercepts and random linear time trends, *as well as* random quadratic time trends.

```
. infile PatientID IMPS79 Week treatment sex ///
> using SCHIZREP.DAT.txt, clear
(1,603 observations read)
.
. generate Week2 = Week*Week
.
. * Quadratic effect of week -- population-level and random
. mixed IMPS79 Week Week2 || PatientID: Week Week2, covariance(unstructured) ml
> e

Performing EM optimization ...

Performing gradient-based optimization:
Iteration 0:  Log likelihood = -2351.3368
Iteration 1:  Log likelihood = -2349.9051
Iteration 2:  Log likelihood = -2349.8716
Iteration 3:  Log likelihood = -2349.8712
Iteration 4:  Log likelihood = -2349.8712

Computing standard errors ...

Mixed-effects ML regression                     Number of obs    =  1,603
Group variable: PatientID                       Number of groups =    437
                                                Obs per group:
                                                              min =      2
                                                              avg =    3.7
                                                              max =      5
```

```
                                                Wald chi2(2)     =  566.68
Log likelihood = -2349.8712                     Prob > chi2      =  0.0000

------------------------------------------------------------------------------
      IMPS79 | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
        Week |  -.5839839   .0415987   -14.04   0.000    -.6655159   -.5024519
       Week2 |   .0427972   .0061063     7.01   0.000      .030829    .0547654
       _cons |   5.275075   .0410982   128.35   0.000     5.194524    5.355627
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects parameters  |   Estimate   Std. err.     [95% conf. interval]
-----------------------------+------------------------------------------------
PatientID: Unstructured      |
                   var(Week) |   .3288713   .0605652      .2292282    .4718282
                  var(Week2) |     .00529   .0013594      .0031968    .0087539
                  var(_cons) |    .307313   .0581129      .2121382    .4451877
             cov(Week,Week2) |  -.0393589   .0088374     -.0566799   -.0220379
             cov(Week,_cons) |   .1297501   .0415439      .0483256    .2111747
            cov(Week2,_cons) |  -.0238834    .005853     -.0353551   -.0124117
-----------------------------+------------------------------------------------
               var(Residual) |   .5190102   .0371969      .4509945    .5972835
------------------------------------------------------------------------------
LR test vs. linear model: chi2(6) = 618.98                Prob > chi2 = 0.0000

Note: LR test is conservative and provided only for reference.
```

As seen above, the model with random intercepts and random linear time trends has a log likelihood of -2408.8416, and the model with random intercepts, random linear time trends, *and* random quadratic time trends has a log likelihood of -2349.8712. So, the likelihood ratio χ^2 statistic is $\text{LR}\,\chi^2 \approx -2 \times (-2408.8416 - (-2349.8712)) = 117.9408$. Since we are testing the null hypothesis $H_0 : \sigma^2_{\upsilon_2} = \sigma_{\upsilon_0\upsilon_2} = \sigma_{\upsilon_1\upsilon_2} = 0$, we test the significance of this χ^2 statistic using the chi-bar-squared test with two and three degrees of freedom:

```
. display(0.5*chi2tail(2, 117.9408) + 0.5*chi2tail(3, 117.9408))
1.194e-25
```

Since $p = 1.194 \times 10^{-25} < 0.001$, there is statistically significant heterogeneity in participants' quadratic trends of IMPS Item 79 score over time.

3.3 Final Model

Thus far, we have shown that (1) there is statistical evidence for a linear trend in IMPS Item 79 scores over time, both at the population and individual levels, and moreover, (2) there is statistical evidence for a quadratic trend in IMPS Item 79 scores over time, both at the population and individual levels. As such, our final mixed model is as follows:

Within-Subjects Model:

$$IMPS_{ij} = b_{0i} + b_{1i} \cdot Time_{ij} + b_{2i} \cdot Time_{ij}^2 + \varepsilon_{ij}$$

where:

- $i = 1, ..., 437$ individuals, and
- $j = 1, ..., n_i$ observations ($0 \leq n_i \leq 7$) for patient i,

and

- b_{0i} is the Week 0 IMPS Item 79 score for patient i,
- b_{1i} is the weekly linear change in IMPS Item 79 score for patient i, and
- b_{2i} is he weekly quadratic change in IMPS Item 79 score for patient i.

Between-Subjects Model:

$$\begin{aligned} b_{0i} &= \beta_0 + \upsilon_{0i} \\ b_{1i} &= \beta_1 + \upsilon_{1i} \\ b_{2i} &= \beta_2 + \upsilon_{2i} \end{aligned}$$

where:

- β_0 is the average Week 0 IMPS Item 79 score across all participants,
- υ_{0i} is individual i's deviation from the average Week 0 IMPS Item 79 score,
- β_1 is the average weekly linear change in IMPS Item 79 score across all participants,
- υ_{1i} is individual i's deviation from the average weekly linear change in IMPS Item 79 score,
- β_2 is the average weekly quadratic change in IMPS Item 79 score across all participants, and
- υ_{2i} is individual i's deviation from the average weekly quadratic change in IMPS Item 79 score.

As summarized above, we have found statistically significant estimates of β_0, β_1, and β_2, meaning there is evidence that at the population level, IMPS Item 79 scores change with both linear and quadratic components over time. Moreover, we have found that there is statistically significant heterogeneity in υ_{0i}, υ_{1i}, and υ_{2i} across participants, meaning that participants had statistically significant deviations from the population average IMPS79 starting scores, linear changes in IMPS79 over time, and quadratic changes in IMPS79 over time.

4 Question 3

Now, investigate whether there is evidence for differential trend due to treatment group. Perform an analysis including the mean effect of treatment and any treatment by time interactions that you see fit. Describe the significance of these additional model parameters and what they may suggest about the idea of better living through chemistry. Write down both the within-subjects and between-subjects components for your final model. Describe the meaning of the various model parameters. Obtain the means across time for the two treatment groups and compare these with the estimated means derived from your final model. How well does this model fit the observed means? Use Stata or graph paper (or some other program) to plot the observed means for both groups against the estimated means for Weeks 0, 1, 3, and 6.

4.1 Exploration of Various Models

First, we augment our final model from Question 2 (i.e., including linear and quadratic time trends with individual-level variation in each) with a treatment group dummy, allowing us to assess whether the treatment and placebo groups may have started at different average IMPS Item 79 scores. As shown in the output below, the coefficient estimate on the treatment dummy is statistically significant, suggesting that the treatment and placebo groups had distinct average starting levels of schizophrenia as measured by IMPS79.

```
. infile PatientID IMPS79 Week treatment sex ///
> using SCHIZREP.DAT.txt, clear
(1,603 observations read)
.
. generate Week2 = Week*Week
.
. * Quadratic effect of week and treatment (dummy)
. mixed IMPS79 Week Week2 treatment || PatientID: Week Week2, covariance(unstru
> ctured) mle

Performing EM optimization ...
```

```
Performing gradient-based optimization:
Iteration 0:  Log likelihood = -2346.6686
Iteration 1:  Log likelihood = -2345.2875
Iteration 2:  Log likelihood = -2345.2594
Iteration 3:  Log likelihood = -2345.2592
Iteration 4:  Log likelihood = -2345.2592

Computing standard errors ...

Mixed-effects ML regression                     Number of obs    =  1,603
Group variable: PatientID                       Number of groups =    437
                                                Obs per group:
                                                              min =      2
                                                              avg =    3.7
                                                              max =      5
                                                Wald chi2(3)     = 579.45
Log likelihood = -2345.2592                     Prob > chi2      = 0.0000

------------------------------------------------------------------------------
      IMPS79 | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
        Week |  -.5852446   .0415289   -14.09   0.000    -.6666398   -.5038493
       Week2 |   .0431029   .0060946     7.07   0.000     .0311576    .0550481
   treatment |  -.2894847   .0892219    -3.24   0.001    -.4643564    -.114613
       _cons |   5.493483   .0790312    69.51   0.000     5.338584    5.648381
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects parameters  |   Estimate   Std. err.     [95% conf. interval]
-----------------------------+------------------------------------------------
PatientID: Unstructured      |
                   var(Week) |   .3255113   .0604122      .2262508    .4683192
                  var(Week2) |   .0052151   .0013562      .0031326    .0086818
                  var(_cons) |   .3201282   .0596948      .2221258    .4613695
             cov(Week,Week2) |  -.0388606   .0088156     -.0561389   -.0215823
             cov(Week,_cons) |   .1035736   .0429034      .0194846    .1876627
            cov(Week2,_cons) |  -.0214516   .0059507     -.0331147   -.0097885
-----------------------------+------------------------------------------------
               var(Residual) |   .5200687   .0373244      .4518263    .5986183
------------------------------------------------------------------------------
LR test vs. linear model: chi2(6) = 552.69                Prob > chi2 = 0.0000

Note: LR test is conservative and provided only for reference.
```

We now update this model to include a treatment-week interaction variable, which accounts

for the possibility that the linear time trend in IMPS Item 79 scores differs between the treatment and placebo groups. As shown in the output below, the treatment-week coefficient estimate is negative and statistically significant, but the main effect of treatment is not statistically significant anymore. Intuitively, this implies that at the outset of the study, the treatment and placebo groups did not have statistically distinguishable average IMPS79 scores, but over the course of the study, the linear improvement of the treatment group's scores was faster than the placebo group's. Given that participants were (presumably) randomly assigned to the treatment or placebo groups, this model makes much more intuitive sense than the model above: in a study with random assignment, we would not expect the treatment and control groups' average starting points to be very different from one another, and the above model only suggested that this was the case because it could not ascribe the groups' differences in IMPS79 scores to group-specific time trends.

```
. infile PatientID IMPS79 Week treatment sex ///
> using SCHIZREP.DAT.txt, clear
(1,603 observations read)
.
. generate Week2 = Week*Week
. generate trt_week = treatment*Week
.
. * Quadratic effect of week + treatment
. mixed IMPS79 Week Week2 treatment trt_week || PatientID: Week Week2, covarian
> ce(unstructured) mle

Performing EM optimization ...

Performing gradient-based optimization:
Iteration 0:  Log likelihood = -2321.6201
Iteration 1:  Log likelihood = -2320.4949
Iteration 2:  Log likelihood =  -2320.473
Iteration 3:  Log likelihood = -2320.4729

Computing standard errors ...

Mixed-effects ML regression                     Number of obs    =  1,603
Group variable: PatientID                       Number of groups =    437
                                                Obs per group:
                                                              min =      2
                                                              avg =    3.7
                                                              max =      5
                                                Wald chi2(4)     = 706.45
Log likelihood = -2320.4729                     Prob > chi2      = 0.0000

------------------------------------------------------------------------------
      IMPS79 | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
```

```
-------------+----------------------------------------------------------------
        Week |  -.4174485   .0465501    -8.97   0.000    -.5086851   -.3262119
       Week2 |    .044432   .0060405     7.36   0.000     .0325928    .0562712
   treatment |  -.0616636   .0944304    -0.65   0.514    -.2467437    .1234165
    trt_week |  -.2251362   .0309228    -7.28   0.000    -.2857437   -.1645286
       _cons |   5.321807   .0822018    64.74   0.000     5.160694    5.482919
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects parameters  |   Estimate   Std. err.     [95% conf. interval]
-----------------------------+------------------------------------------------
PatientID: Unstructured      |
                   var(Week) |   .2901765   .0578713      .1962923    .4289646
                  var(Week2) |   .0049764   .0013293      .0029481       .0084
                  var(_cons) |   .3082947   .0580882      .2131006    .4460131
              cov(Week,Week2) |  -.0359407   .0085515     -.0527012   -.0191801
              cov(Week,_cons) |   .1251116   .0409641      .0448235    .2053998
             cov(Week2,_cons) |   -.022689   .0058454     -.0341458   -.0112323
-----------------------------+------------------------------------------------
               var(Residual) |   .5182238   .0370876      .4504012    .5962592
------------------------------------------------------------------------------
LR test vs. linear model: chi2(6) = 568.63                Prob > chi2 = 0.0000

Note: LR test is conservative and provided only for reference.
```

Finally, we consider a model that includes a treatment dummy variable, a treatment-week interaction, *and* a treatment-week-squared interaction. We recover statistically significant coefficients on the treatment-week and treatment-week-squared interactions, suggesting that the treatment and placebo groups' average IMPS79 scores have distinct linear and quadratic trends over time. We again find that the coefficient on the treatment dummy is not significant, which indicates that while the groups had different trends in IMPS79 scores over time, the average starting scores of the two groups were not statistically distinguishable. However, the main quadratic effect is not statistically significant anymore, which implies that while the treatment group's IMPS79 scores had a curvelinear time trend, the placebo group's IMPS79 time trend was purely linear.

```
. infile PatientID IMPS79 Week treatment sex ///
> using SCHIZREP.DAT.txt, clear
(1,603 observations read)
.
. generate Week2 = Week*Week
. generate trt_week = treatment*Week
. generate trt_week2 = treatment*Week*Week
.
```

```
. * Quadratic effect of week + treatment
. mixed IMPS79 Week Week2 treatment trt_week trt_week2 || PatientID: Week Week2
> , covariance(unstructured) mle

Performing EM optimization ...

Performing gradient-based optimization:
Iteration 0:  Log likelihood = -2316.9487
Iteration 1:  Log likelihood = -2315.8454
Iteration 2:  Log likelihood = -2315.8127
Iteration 3:  Log likelihood = -2315.8123
Iteration 4:  Log likelihood = -2315.8123

Computing standard errors ...

Mixed-effects ML regression                     Number of obs     =  1,603
Group variable: PatientID                       Number of groups  =    437
                                                Obs per group:
                                                              min =      2
                                                              avg =    3.7
                                                              max =      5
                                                Wald chi2(5)      = 720.98
Log likelihood = -2315.8123                     Prob > chi2       = 0.0000

------------------------------------------------------------------------------
      IMPS79 | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
        Week |  -.2087056   .0822949    -2.54   0.011    -.3700006   -.0474105
       Week2 |   .0109578   .0124576     0.88   0.379    -.0134585    .0353742
   treatment |  -.0186494   .0953924    -0.20   0.845    -.2056151    .1683162
    trt_week |  -.4982512   .0942799    -5.28   0.000    -.6830364   -.3134661
   trt_week2 |   .0435435   .0142123     3.06   0.002     .0156878    .0713991
       _cons |   5.288397   .0828515    63.83   0.000     5.126012    5.450783
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects parameters  |   Estimate   Std. err.     [95% conf. interval]
-----------------------------+------------------------------------------------
PatientID: Unstructured      |
                   var(Week) |   .2800558   .0569251      .1880297    .4171216
                  var(Week2) |   .0047693   .0013091      .0027849    .0081676
                  var(_cons) |   .3073231   .0579818      .2123251    .4448247
             cov(Week,Week2) |  -.0345033   .0084138     -.0509939   -.0180126
             cov(Week,_cons) |   .1280959   .0404081      .0488974    .2072944
            cov(Week2,_cons) |  -.0232647   .0057597     -.0345535   -.0119758
```

```
------------------------------+------------------------------------------------
               var(Residual) |   .5177322   .0370136      .4500402    .5956061
------------------------------------------------------------------------------
LR test vs. linear model: chi2(6) = 570.43                Prob > chi2 = 0.0000

Note: LR test is conservative and provided only for reference.
```

4.2 Final Model

We adopt the last model above as our final model:

Within-Subjects Model:

$$IMPS_{ij} = b_{0i} + b_{1i} \cdot Time_{ij} + b_{2i} \cdot Time_{ij}^2 + \varepsilon_{ij}$$

where:

- $i = 1, ..., 437$ individuals, and
- $j = 1, ..., n_i$ observations ($0 \leq n_i \leq 7$) for patient i,

and

- b_{0i} is the Week 0 IMPS Item 79 score for patient i,
- b_{1i} is the weekly linear change in IMPS Item 79 score for patient i, and
- b_{2i} is he weekly quadratic change in IMPS Item 79 score for patient i.

Between-Subjects Model:

$$\begin{aligned} b_{0i} &= \beta_0 + \beta_3 \cdot trt_i + \upsilon_{0i} \\ b_{1i} &= \beta_1 + \beta_4 \cdot trt_i + \upsilon_{1i} \\ b_{2i} &= \beta_2 + \beta_5 \cdot trt_i + \upsilon_{2i} \end{aligned}$$

where:

- β_0 is the average Week 0 IMPS Item 79 score among participants in the placebo group,
- β_3 is the difference in average Week 0 IMPS Item 79 scores between participants in the treatment and placebo groups,
- υ_{0i} is individual i's deviation from the average Week 0 IMPS 79 score within their group (treatment or placebo),
- β_1 is the average weekly linear change in IMPS Item 79 score among participants in the placebo group,

- β_4 is the difference in the average linear change in IMPS Item 79 scores between participants in the treatment and placebo groups,
- υ_{1i} is individual i's deviation from the average weekly linear change in IMPS Item 79 score within their group (treatment or placebo),
- β_2 is the average weekly quadratic change in IMPS Item 79 score among participants in the placebo group,
- β_5 is the difference in the average quadratic change in IMPS Item 79 scores between participants in the treatment and placebo groups, and
- υ_{2i} is individual i's deviation from the average weekly quadratic change in IMPS Item 79 score within their group (treatment or placebo).

As stated above, we recovered statistically significant negative coefficients on `Week` and the `trt_week` interaction term, and a statistically significant positive coefficient on the `trt_week2` interaction term. Collectively, this suggests that while schizophrenic symptamology may improve without pharmaceutical intervention (c.f., the coefficient on `Week` was negative and statistically significant), this improvement can be made much faster by taking the drugs tested in this study (c.f., the coefficient on the `trt_week` interaction was negative and statistically significant). However, the benefits of pharmaceutical treatment diminish over time, such that a patient's rate of improvement decelerates the longer they are treated (c.f., the coefficient on the `trt_week2` interaction was positive and statistically significant).

4.3 Model Fit: Observed vs. Estimated Means

The table below summarizes the observed mean IMPS79 scores for the placebo (left) and treatment (right) groups at each week of the study.

```
. infile PatientID IMPS79 Week treatment sex ///
> using SCHIZREP.DAT.txt, clear
(1,603 observations read)
. tabulate Week treatment, summarize(IMPS79) nostandard nofreq wrap

                           Means of IMPS79

           |      treatment
      Week |         0          1 |     Total
-----------+----------------------+----------
         0 | 5.3523364  5.3715596 | 5.3668203
         1 | 4.9904762  4.4333333 | 4.5706573
         2 |       5.8  3.2777778 | 4.1785714
         3 | 4.7390805  3.8020906 | 4.0200535
         4 |       5.5  2.5333333 | 3.0727273
         5 |      4.25  2.9285714 | 3.2222222
```

```
         6 | 4.2457143  3.0630189 | 3.3101493
-----------+----------------------+----------
     Total | 4.9066138  4.2084082 | 4.3730505
```

Now, the table below summarizes the estimated/fitted mean IMPS79 scores for the placebo (left) and treatment (right) groups at each week of the study. (Note that the row numbers begin at 1, not 0, due to mata formatting.)

```
. mata
------------------------------------------------- mata (type end to exit) -----
: /* beta estimates */
: beta = (5.288397 \
>         -.2087056 \
>         .0109578 \
>         -.0186494 \
>         -.4982512 \
>         .0435435)

:
: /* design matrix for placebo group */
: xmat0 = (1, 0, 0, 0, 0, 0 \
>          1, 1, 1, 0, 0, 0 \
>          1, 2, 4, 0, 0, 0 \
>          1, 3, 9, 0, 0, 0 \
>          1, 4, 16, 0, 0, 0 \
>          1, 5, 25, 0, 0, 0 \
>          1, 6, 36, 0, 0, 0)

:
: /* design matrix for treatment group */
: xmat1 = (1, 0, 0, 1, 0, 0 \
>          1, 1, 1, 1, 1, 1 \
>          1, 2, 4, 1, 2, 4 \
>          1, 3, 9, 1, 3, 9 \
>          1, 4, 16, 1, 4, 16 \
>          1, 5, 25, 1, 5, 25 \
>          1, 6, 36, 1, 6, 36)

:
: /* fitted values for placebo and treatment groups */
: xbeta0 = xmat0*beta

: xbeta1 = xmat1*beta
```

```
:
: xbeta0, xbeta1
                1           2
    +------------------------+
  1 |   5.288397   5.2697476  |
  2 |  5.0906492   4.6172921  |
  3 |   4.914817   4.0738392  |
  4 |  4.7609004   3.6393889  |
  5 |  4.6288994   3.3139412  |
  6 |   4.518814   3.0974961  |
  7 |  4.4306442   2.9900536  |
    +------------------------+

:
: end
--------------------------------------------------------------------------------
```

Observe that for Weeks 0, 1, 3, 5, and 6, the fitted means for each group are fairly close to the actual means, with errors falling between roughly 0.02 and 0.25. For Weeks 2 and 4, the errors are much larger, generally falling between 0.8 and 0.9. However, this can most likely be attributed to the small number of observations during Weeks 2 and 4 creating sample bias; that there were not similarly large errors for our Week 5 estimates (where there was also a small number of observations) is likely just a fluke. We visualize the observed vs. estimated means for each group (excluding Weeks 2, 4, and 5, whose averages were based on small samples) in the figure below.