Modeling Utilities over Time

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Objectives

- To describe how to analyze health-related quality of life (HRQoL) data with multiple observations over time

Outline

- **Introduction to longitudinal modeling**
  - Study design
  - Longitudinal models
- Real-world example: Modeling the change in health-related quality of life (HRQoL) in patients with advanced HIV (OPTIMA trial)
  - OPTIMA
  - Exploratory analysis
  - Model

Ask the Audience (whiteboard)

■ What studies have you been involved with that have measured change (in HRQoL or other outcomes)?

Study Design

- Checklist for designing health-related quality of life (HRQoL) studies
    1. Rationale for studying HRQoL
    2. Explicit research objectives
    3. Strategies to limit the exclusion of subjects
    4. Rationale for timing of assessments and off-study rules
    5. Rationale for instrument selection
    6. Minimizing bias and missing data
    7. Analytic plan

Fairclough DL. *Design and Analysis of Quality of Life Studies in Clinical Trials.* 1st ed. Boca Raton, FL: Chapman and Hall/CRC Press; 2002.

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  - Study design
  - <u>Longitudinal models</u>

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# 3 Important Features of Longitudinal Studies

1. Multiple waves of data

2. Sensible metric for time

3. Outcomes that change systematically over time

   – Precision of outcomes must be equatable over time

   – Outcomes must be equally valid over time

   – Preserve outcome precision over time

Repeated Measures Models

- Applicable to studies where…
  - Subjects are experiencing the same condition
  - Assessments correspond to an event or intervention phase
  - Assessments are limited (< 4) with time conceptualized as a categorical variable

Repeated Measures Models (cont'd)
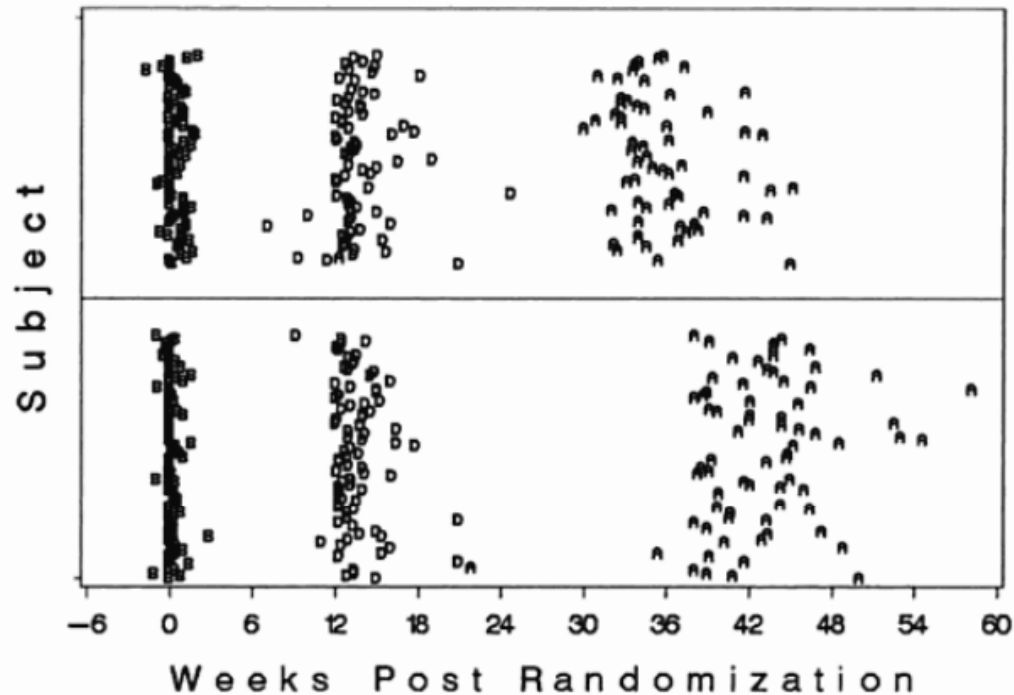
Figure 1.2. Timing of observations in a study with an event-driven design with assessments before (B), during (D), and 4 months after (A) therapy. Data are from the adjuvant breast cancer study [41]. Each row corresponds to a randomized subject. Subjects randomized to the 16-week regimen appear in the upper half of the figure and subjects randomized to the CAF regiment are in the lower half of the figure.

Fairclough DL. *Design and Analysis of Quality of Life Studies in Clinical Trials.* 1st ed. Boca Raton, FL: Chapman and Hall/CRC Press; 2002.

Repeated Measures Models – Drawbacks

- Assessments may not take place when scheduled.

Repeated Measures Models – Drawbacks (cont'd)
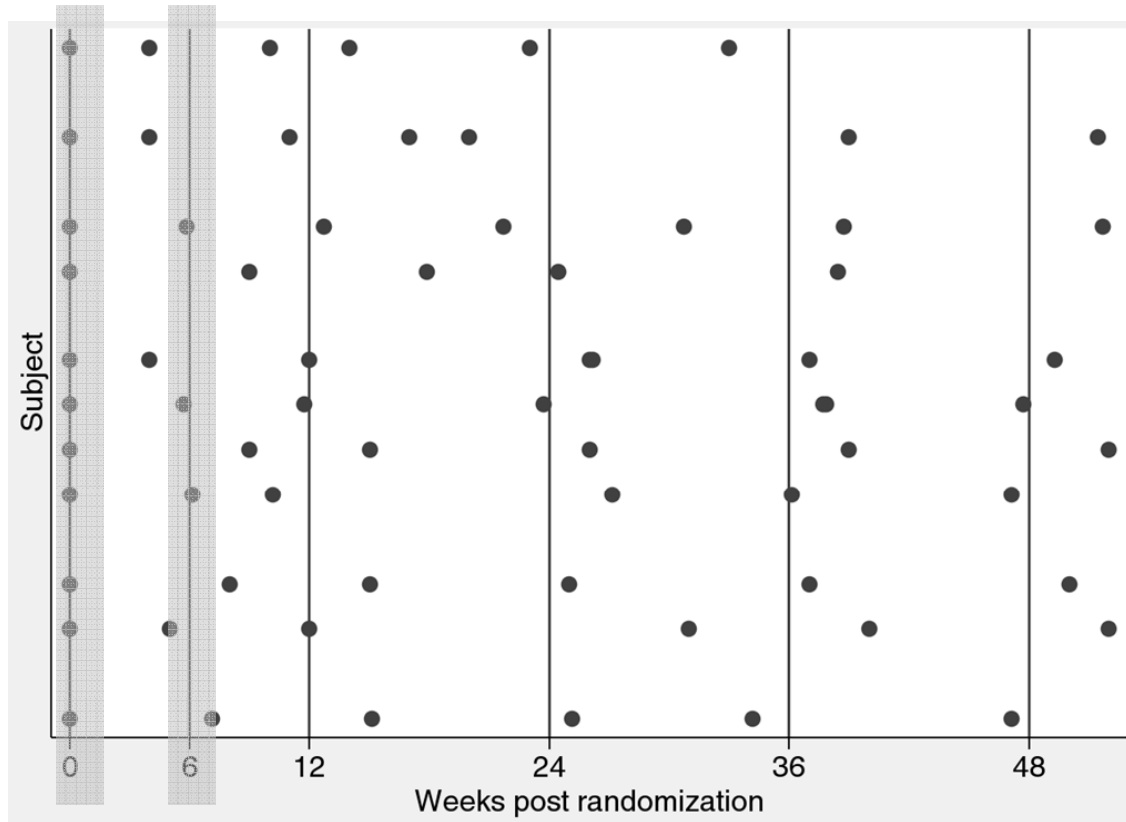
- Timing of observations for 1 site over 1 year in the OPTIMA trial

History of Growth Curve Models

- 1980s = development of statistical models
- Various names
  - Individual growth curve models
  - Random coefficient models
  - Hierarchical linear models
  - Multilevel models
  - Mixed models
- Describe changes in height and weight as a function of age in children.

Why Not Use OLS?

- Ordinary least squares (OLS) regression assumes that observations are independent

- Biased standard errors

- Growth curve models can handle correlated errors

Definition of a Growth Curve Model

- Change over time in a phenomenon of interest (e.g. quality of life) at both the individual and aggregate levels.

- 2 types of questions about change:

  Level 1: **Within-person** change (how individuals change over time)

  Time-varying predictors (e.g. days since randomization)

  Level 2: **Between-person** differences in change (how changes vary across individuals)

  Time-invariant predictors (e.g. randomization group)

Level 1 Submodel – Within-Person

$$Y_{ij} = \left[\pi_{0i} + \pi_{1i}(time_{ij})\right] + \left[\varepsilon_{ij}\right]$$

Y_{ij} =   The outcome of interest (for subject i at time j)

π_{0i} =   Intercept, or subject i's true value of QoL at baseline

π_{1i} =   Slope, or subject i's rate of change in true QoL

ε_{ij} =   Residual or random measurement error

Level 2 Submodels – Between-Person

$$Y_{ij} = \left[\boxed{\pi_{0i}} + \boxed{\pi_{1i}}(time_{ij}) \right] + \left[\varepsilon_{ij} \right]$$

Level 1 model

$$\boxed{\pi_{0i}} = \boxed{\gamma_{00} + \gamma_{01}INTVN + \zeta_{0i}}$$

Level 2 submodels

$$\boxed{\pi_{1i}} = \boxed{\gamma_{10} + \gamma_{11}INTVN + \zeta_{1i}}$$

ITVN = Intervention

γ_{00} = Population intercept
γ_{01} = Deviation from population intercept
ζ_{0i} = Residual

γ_{10} = Population slope
γ_{11} = Deviation from population slope
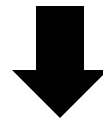ζ_{1i} = Residual

Integrated Growth Curve Model

$$Y_{ij} = \left[\pi_{0i} + \pi_{1i}(time_{ij}) \right] + \left[\varepsilon_{ij} \right] \text{Level 1 model}$$
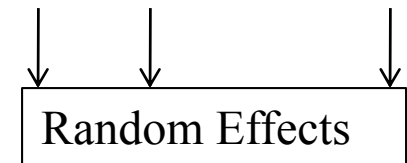
$$\pi_{0i} = \gamma_{00} + \gamma_{01}INTVN + \zeta_{0i}$$

$$\pi_{1i} = \gamma_{10} + \gamma_{11}INTVN + \zeta_{1i} \qquad \text{Level 2 submodels}$$

$$Y_{ij} = \left[(\gamma_{00} + \gamma_{10}TIME_{ij} + \gamma_{01}INTVN_i + \gamma_{11}(INTVN_i \times TIME_{ij}) \right] + \left[\zeta_{0i} + \zeta_{1i}TIME_{ij} + \varepsilon_{ij} \right]$$

Fixed Effects

Random Effects
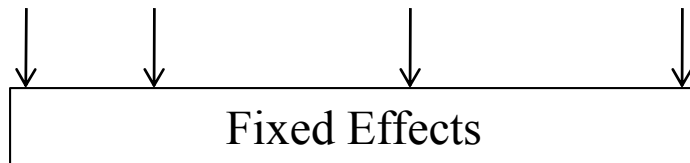
Advantages of Growth Curve Models

■ Advantages

– Data modeled at the individual level

– Flexible time variable

– Easy handling of missing data

– Easily incorporate data nesting/clustering

Outline

■ Introduction to longitudinal modeling
  – Study design
  – Longitudinal models

■ <u>Real-world example: Modeling the change in health-related quality of life (HRQoL) in patients with advanced HIV (OPTIMA trial)</u>
  – <u>OPTIMA</u>
  – Exploratory analysis
  – Model

OPTIMA

- Effective antiretroviral therapy (ART) improves survival in HIV-infected patients.
- The optimal management strategy for advanced HIV patients infected with multi-drug resistant HIV is unclear.
- CSP #512, Options in Management with Antiretrovirals
- 2x2 open randomized study
- UK, Canada, and US
- June 2001 - December 2007
- 368 patients randomized

		Antiretroviral therapy **intensification**	
		Control ($\leq$ 4 drugs)	Experiment ($\geq$ 5 drugs)
12 week antiretroviral therapy **interruption**	Control	Neither	1
	Experiment	1	Both

Research Questions

- What is the longitudinal effect of treatment interruption and ART intensification therapies on HRQoL in a multi-drug resistant HIV-1 infected patient population?

- Does HRQoL improve for patients randomized to the interruption group during the interruption period?

Outcomes

■ Primary and secondary outcomes

– Time to first AIDS-defining event or death

– Time to first serious adverse event

■ Other sociodemographic and clinical data (e.g. age, sex, transmission risk group, etc.)

Outcomes (cont'd)

- Health-Related Quality of Life (HRQoL)
  - Baseline, 6, 12, 24, every 12 weeks thereafter
  - <u>Health Utilities Index Mark 3 (HUI3)</u>
  - EQ-5D
  - Visual analog scale
  - Medical Outcomes Study HIV Health Survey
  - Standard gamble (SG) (US patients only)
  - Time trade-off (TTO) (US patients only)
  - 5,141 HRQoL assessments over 6.25 years of follow-up (median 3.2 years)

HRQoL Outcome: Health Utilities Index Mark 3 (HUI3)

- Preference/utility-based instrument
- 8 attributes, each with 5–6 levels
- 972,000 possible health states.
- Weights are estimated with valuation data from a sample of adults in Hamilton, Ontario, Canada
- Utilities range from -0.36 to 1

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Ask the Audience

- Why is missing data a problem?

Missing Data

- Why is missing data a problem?
  - Loss of statistical power
  - Bias of estimates
- At baseline, 4% of HUI3 assessments in the OPTIMA trial were missing.
- Plots to describe missingness
  - Average QoL scores by time of drop-out
  - Average QoL scores by time to death
  - Average QoL scores by % missing over time

Mean HUI3 by Visit Week, Patients Grouped by When They Were Lost to Follow-Up
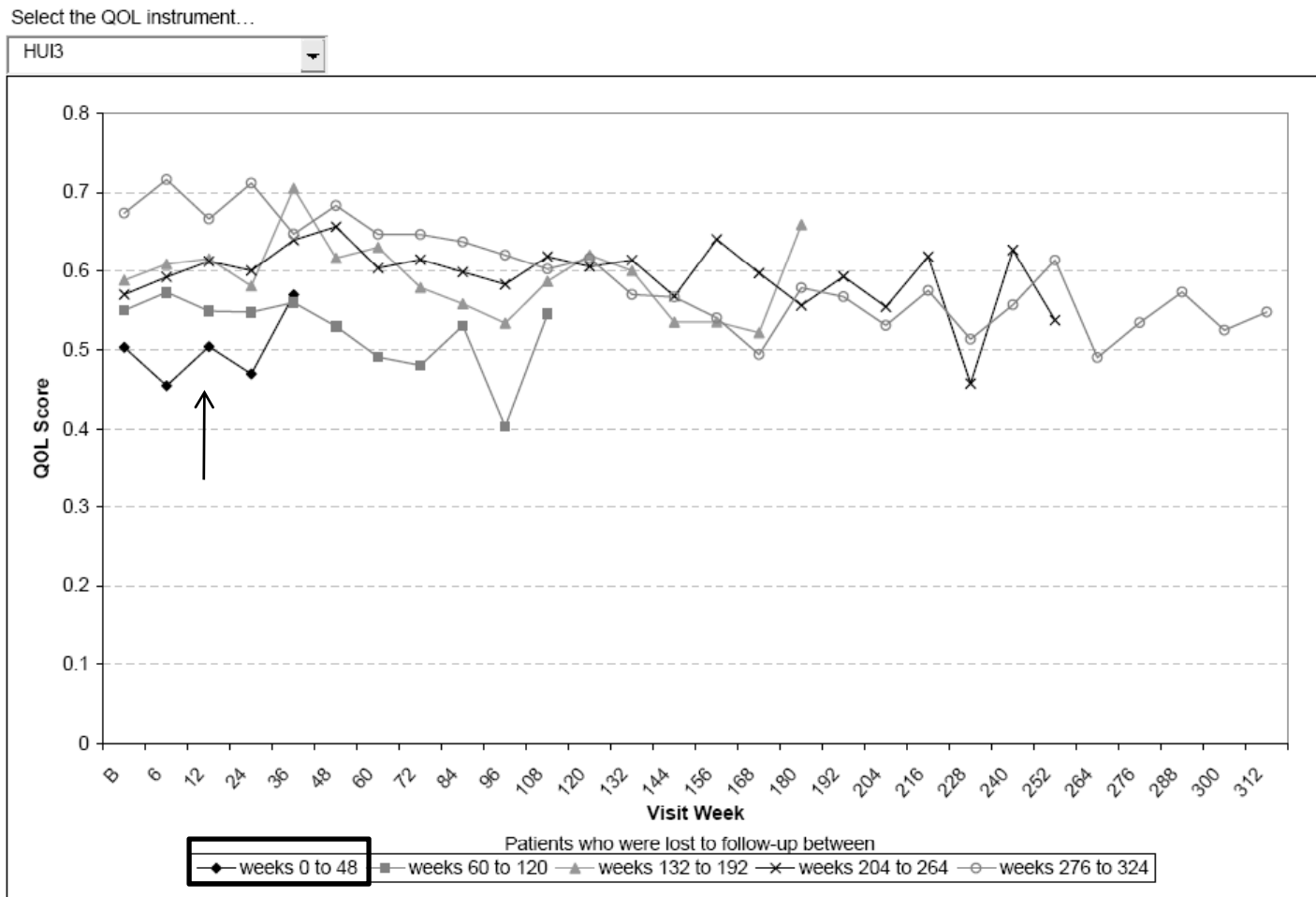
Missing Data

- Other patterns/mechanisms?
  - Do baseline characteristics predict drop-out?
    - Proportional hazards model (PROC PHREG)
  - Are "skippers" - patients with intermittent QOL assessments – different from those with few skipped assessments?
    - Regressions (PROC REG)
  - Are certain clinical events associated with "missing" QoL assessments?
    - Generalized linear mixed model (PROC GLIMMIX)

Missing Data

- ## What next?
  - Serious adverse events predicted missing HRQoL data in the OPTIMA trial.
  - BUT, serious adverse events were distributed equally among the randomization groups.
  - Missing data left "as is".
  - Other QoL studies, where missing data are not ignorable?
    - Consider imputation as part of your sensitivity analyses.
    - Fairclough 2002, Ch. 7, Multiple Imputation

Person-Period Data (Long-Format)

- Each subject has multiple records, one per assessment

Person-Period (Long)

ID	HUI3	MONTHS FROM RAND	MALE
1	.80	0	1
1	.85	1	1
1	.97	2	1
2	.65	0	0
2	.77	1	0
2	.75	2	0
3	.99	0	1

Person-Level (Wide)

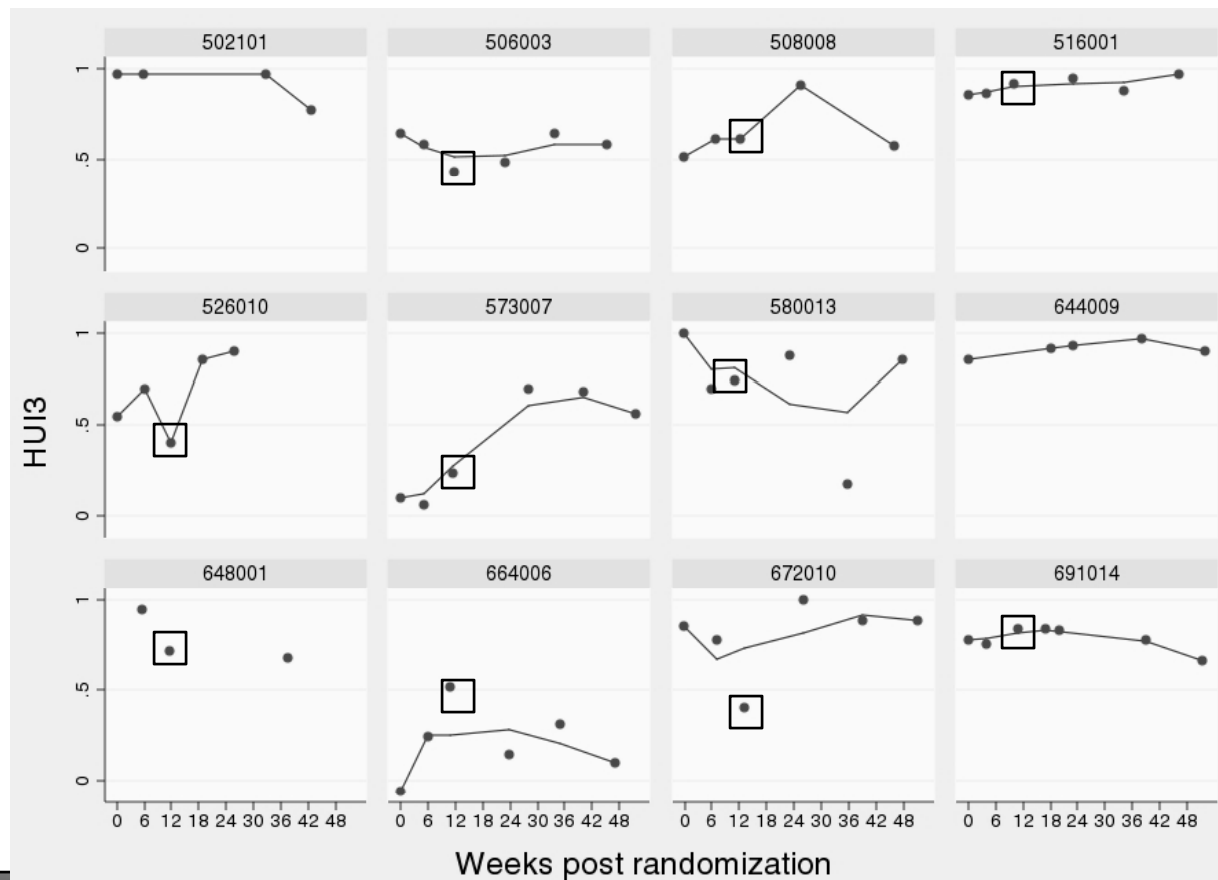| ID	HUI3_ MONTH_0	HUI3_ MONTH_1	HUI3_ MONTH_2	MALE
1	.80	.85	.97	1
2	.65	.77	.75	0
3	.99	.	.	1

- Reshape from wide to long?
  - UCLA Academic Technology Service

Level 1: Within-Person Change over Time

$$Y_{ij} = \left[\pi_{0i} + \pi_{1i}(time_{ij})\right] + \left[\varepsilon_{ij}\right]$$

Level 1 model

Figure 1. Empirical growth plots for select OPTIMA patients. Smooth nonparametric trajectories superimposed.

Level 2: Differences in Change Across People

$$\pi_{0i} = \gamma_{00} + \gamma_{01} INTVN + \zeta_{0i}$$

$$\pi_{1i} = \gamma_{10} + \gamma_{11} INTVN + \zeta_{1i}$$

Level 2 submodels
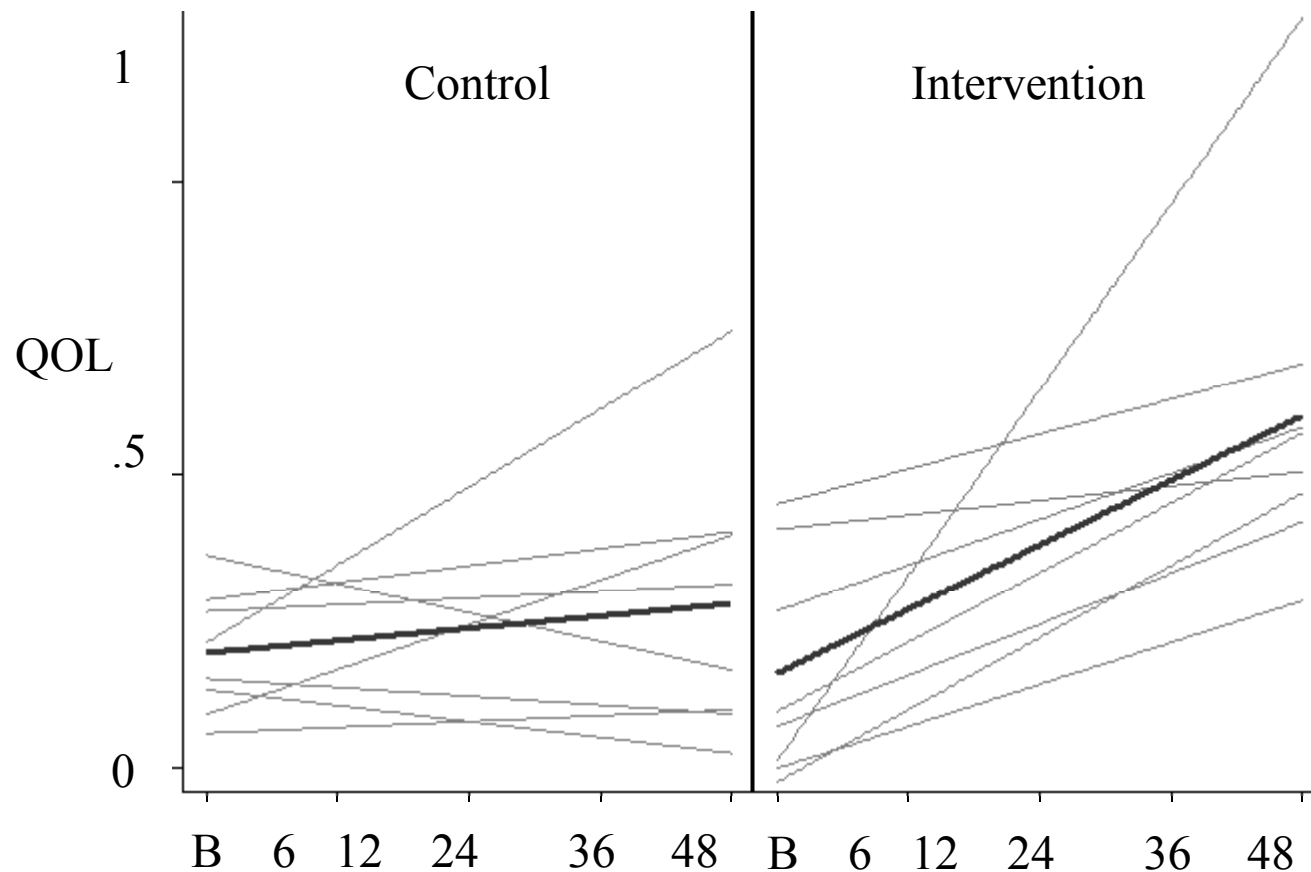
For illustrative purposes only. NOT actual OPTIMA data.

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From Research Question to Model

- What is the longitudinal effect of treatment interruption and ART intensification therapies on HRQoL in a multi-drug resistant HIV-1 infected patient population?

- Does HRQoL improve for patients randomized to the interruption group during the interruption period?

Dependent variable?   HUI3

Independent variables?   Time   Both Interruption and Intensification

Treatment Interruption   First quarter of the trial

Treatment Intensification

OPTIMA Model

$$Y_{ij} = \left[(\gamma_{00} + \gamma_{10} TIME_{ij} + \gamma_{01} INTVN_i + \gamma_{11}(INTVN_i \times TIME_{ij}) \right] + \left[\zeta_{0i} + \zeta_{1i} TIME_{ij} + \varepsilon_{ij} \right]$$

Dependent variable?   HUI3

Independent variables?   Time   Both Interruption and Intensification

Treatment Interruption   First quarter of the trial

Treatment Intensification

$$HUI3_{ij} = \left[(\beta_0 + \beta_1(TIME) + \beta_2(INTERRUPT) + \beta_3(INTENSIFY) + \beta_4(BOTH) + \beta_5(QUARTER1) \right. \\ + \beta_6(INTERRUPT \times QUARTER1) + \beta_7(INTENSIFY \times QUARTER1) + \beta_8(BOTH \times QUARTER1) \\ \left. + \beta_9(BASELINEHUI3) \right] + \left[\varepsilon_{ij} \right]$$

0.5 =   in group
-0.5 = not in group

OPTIMA Model – Other Specifications

1. Ignoring the baseline value

2. Expressing all values as a difference from baseline

3. <u>Including the baseline value as a covariate</u>

OPTIMA Model – SAS code

$$HUI3_{ij} = \begin{bmatrix} (\beta_0 + \beta_1(TIME) + \beta_2(INTERRUPT) + \beta_3(INTENSIFY) + \beta_4(BOTH) + \beta_5(QUARTER1) \\ + \beta_6(INTERRUPT \times QUARTER1) + \beta_7(INTENSIFY \times QUARTER1) + \beta_8(BOTH \times QUARTER1) \\ + \beta_9(BASELINEHUI3) \end{bmatrix} + [\varepsilon_{ij}]$$

```
proc mixed data = qol;            /*1. Evokes mixed procedure, identifies dataset, specifies */
                                  /*    default estimation method or restrict max likelihood*/
where baseline=0;                 /*2. Using follow-up data only; baseline data excluded*/
model hui3 =                      /*3. Dependent variable, QOL instrument HUI3*/
t                                 /*4. Time in years*/
sti_c                             /*5. Interruption group indicator, centered*/
mega_c                            /*6. Intensification group indicator, centered*/
both_c                            /*7. Interruption + intensification group indicator, centered*/
time_q1                           /*8. First quarter of follow-up indicator*/
sti_c*time_q1                     /*9. Interaction term, 5 and 8*/
mega_c*time_q1                    /*10. Interaction term, 6 and 8*/
both_c*time_q1                    /*11. Interaction term, 7 and 8*/
dbase_hui3                        /*12. Baseline value, deviation from the mean HUI3*/
/ solution ddfm=kr;               /*13. Significance tests for all fixed effects and Kenward-*/
                                  /*     Roger method of degrees of freedom*/
random int t /                    /*14. Specifies the intercept and time as random effects*/
subject=newsubj_id                /*15. Specifies observations as nested within Subject ID*/
type=un;                          /*16. Specifies an unstructured variance/covariance matrix*/
                                  /*    for the random effects*/
```

OPTIMA Model – SAS code (cont'd)

$$HUI3_{ij} = \begin{bmatrix} (\beta_0 + \beta_1(TIME) + \beta_2(INTERRUPT) + \beta_3(INTENSIFY) + \beta_4(BOTH) + \beta_5(QUARTER1) \\ + \beta_6(INTERRUPT \times QUARTER1) + \beta_7(INTENSIFY \times QUARTER1) + \beta_8(BOTH \times QUARTER1) \\ + \beta_9(BASELINEHUI3) \end{bmatrix} + [\varepsilon_{ij}]$$

```
estimate "Difference between sti & no sti trend before 3 months" sti_c 1 sti_c*time_q1 1;
estimate "Difference between mega & no mega trend before 3 months" mega_c 1 mega_c*time_q1 1;
estimate "Difference between both & no both trend before 3 months" both_c 1 both_c*time_q1 1;
run;
```

Results

```
The Mixed Procedure


   Covariance Parameter Estimates


Cov Parm        Subject         Estimate
```

Cov Parm	Subject	Estimate	
UN(1,1)	newsubj_id	0.02048	/* Variance estimate for intercept*/
UN(2,1)	newsubj_id	-0.00037	/* Covariance estimate for intercept and slope*/
UN(2,2)	newsubj_id	0.002368	/* Variance estimate for slope*/
Residual		0.02956	/* Level 1 residual*/

```
            Fit Statistics
```

-2 Res Log Likelihood	-1854.4
AIC (smaller is better)	-1846.4
AICC (smaller is better)	-1846.4
BIC (smaller is better)	-1831.1

Results (cont'd)

$$HUI3_{ij} = \begin{bmatrix} (\beta_0 + \beta_1(TIME) + \beta_2(INTERRUPT) + \beta_3(INTENSIFY) + \beta_4(BOTH) + \beta_5(QUARTER1) \\ + \beta_6(INTERRUPT \times QUARTER1) + \beta_7(INTENSIFY \times QUARTER1) + \beta_8(BOTH \times QUARTER1) \\ + \beta_9(BASELINEHUI3) \end{bmatrix} + \begin{bmatrix} \varepsilon_{ij} \end{bmatrix}$$

```
Solution for Fixed Effects
```

Effect	Estimate	Standard Error	DF	t Value	Pr > |t|		
Intercept	0.6288	0.009959	407	63.13	<.0001 /*	β_0	*/
t	-0.01710	0.004214	199	-4.06	<.0001 /*	β_1	*/
sti_c	-0.02380	0.01921	354	-1.24	0.2162 /*	β_2	*/
mega_c	-0.01248	0.01848	358	-0.68	0.5000 /*	β_3	*/
both_c	-0.02958	0.03832	354	-0.77	0.4406 /*	β_4	*/
time_q1	-0.01426	0.009555	3991	-1.49	0.1357 /*	β_5	*/
sti_c*time_q1	-0.02640	0.01870	3983	-1.41	0.1580 /*	β_6	*/
mega c*time q1	0.003552	0.01805	3975	0.20	0.8440 /*	β_7	*/
both_c*time_q1	0.04693	0.03739	3983	1.25	0.2096 /*	β_8	*/
dbase_hui3	0.6801	0.02849	321	23.87	<.0001 /*	β_9	*/

Results (cont'd)

$$HUI3_{ij} = \begin{bmatrix} (\beta_0 + \beta_1(TIME) + \beta_2(INTERRUPT) + \beta_3(INTENSIFY) + \beta_4(BOTH) + \beta_5(QUARTER1) \\ + \beta_6(INTERRUPT \times QUARTER1) + \beta_7(INTENSIFY \times QUARTER1) + \beta_8(BOTH \times QUARTER1) \\ + \beta_9(BASELINEHUI3) \end{bmatrix} + [\varepsilon_{ij}]$$

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > |t|
Difference between sti & no sti trend before 3 months	-0.05019	0.02280	648	-2.20	0.0281
Difference between mega & no mega trend before 3 months	-0.00893	0.02193	655	-0.41	0.6841
Difference between both & no both trend before 3 months	0.01734	0.04553	651	0.38	0.7034

Results (cont'd)

$$HUI3_{ij} = \begin{bmatrix} (\beta_0 + \beta_1(TIME) + \beta_2(INTERRUPT) + \beta_3(INTENSIFY) + \beta_4(BOTH) + \beta_5(QUARTER1) \\ + \beta_6(INTERRUPT \times QUARTER1) + \beta_7(INTENSIFY \times QUARTER1) + \beta_8(BOTH \times QUARTER1) \\ + \beta_9(BASELINEHUI3) \end{bmatrix} + [\varepsilon_{ij}]$$

Effect	Estimate
Intercept	0.6288
t	-0.01710
sti_c	-0.02380
mega_c	-0.01248
both_c	-0.02958
time_q1	-0.01426
sti c*time q1	-0.02640
mega_c*time_q1	0.003552
both_c*time_q1	0.04693
dbase_hui3	0.6801

Interruption group

$$HUI3_{ij} = \begin{bmatrix} (0.6288 + (-0.01710) + (-0.02380)(0.5) + (-0.01248)(-0.5) + (-0.02958)(-0.25) + (-0.01426)(1) \\ + (-0.02640)(0.5)(1) + (0.003552)(-0.5)(1) + (0.04693)(-0.25)(1) \\ + (0.6801) \end{bmatrix} = 1.252567$$

Non interruption group

$$HUI3_{ij} = \begin{bmatrix} (0.6288 + (-0.01710) + (-0.02380)(-0.5) + (-0.01248)(-0.5) + (-0.02958)(-0.25) + (-0.01426)(1) \\ + (-0.02640)(-0.5)(1) + (0.003552)(-0.5)(1) + (0.04693)(-0.25)(1) \\ + (0.6801) \end{bmatrix} = 1.302767$$

Difference in HUI3 score, interruption vs. no interruption group, first quarter of follow-up?

$$1.252567 - 1.302767 = -0.0502$$

Label	Estimate	Error	DF	t Value	Pr > |t|
Difference between sti & no sti trend before 3 months	-0.05019	0.02280	648	-2.20	0.0281
Difference between mega & no mega trend before 3 months	-0.00893	0.02193	655	-0.41	0.6841
Difference between both & no both trend before 3 months	0.01734	0.04553	651	0.38	0.7034

Summary

- Introduction to growth curve modeling.

- Application of growth curve modeling to actual longitudinal quality of life data from OPTIMA.

- Growth curve modeling is powerful and flexible!

Suggested References

- Sinnott PL, Joyce VR, Barnett PG. *Preference Measurement in Economic Analysis*. Guidebook. Menlo Park CA. VA Palo Alto, Health Economics Resource Center; 2007.

- Fairclough DL. *Design and Analysis of Quality of Life Studies in Clinical Trials.* 1st ed. Boca Raton, FL: Chapman and Hall/CRC Press; 2002.

- Singer JD, Willett JB. *Applied Longitudinal Analysis. Modeling Change and Event Occurrence.* 1st ed. New York, NY: Oxford University Press; 2003.
  - http://www.ats.ucla.edu/stat/examples/alda/

- UCLA Academic Technology Service Statistical Computing
  - http://www.ats.ucla.edu/stat/

Questions?

- VA employees:
  http://vaww.infoshare.va.gov/sites/HERC
- Next presentation – May 12, 2010
  - Paul Barnett, Ph.D.
  - "How can Cost Effectiveness Analysis be Made More Relevant to US Health Care?"

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