Modeling Health-Related Quality of Life over Time

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HEALTH SERVICES RESEARCH & DEVELOPMENT

Brief CEA Review

$$\frac{\text{Cost}_{\text{Intervention}} - \text{Cost}_{\text{UsualCare}}}{\text{Outcome}_{\text{Intervention}} - \text{Outcome}_{\text{UsualCare}}}$$

- Quality-Adjusted Life Year (QALY)
  - Length of life weighted by quality of life
  - Utilities, preference-based health-related quality of life (HRQoL)
    - EQ-5D, Health Utilities Index (HUI3), etc.

Objectives

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

Outline

- Introduction to types of longitudinal studies and models
- Real-world example: Modeling the change in health-related quality of life (HRQoL) in patients with advanced HIV
  - OPTIMA
  - Exploratory analysis
  - Models

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)

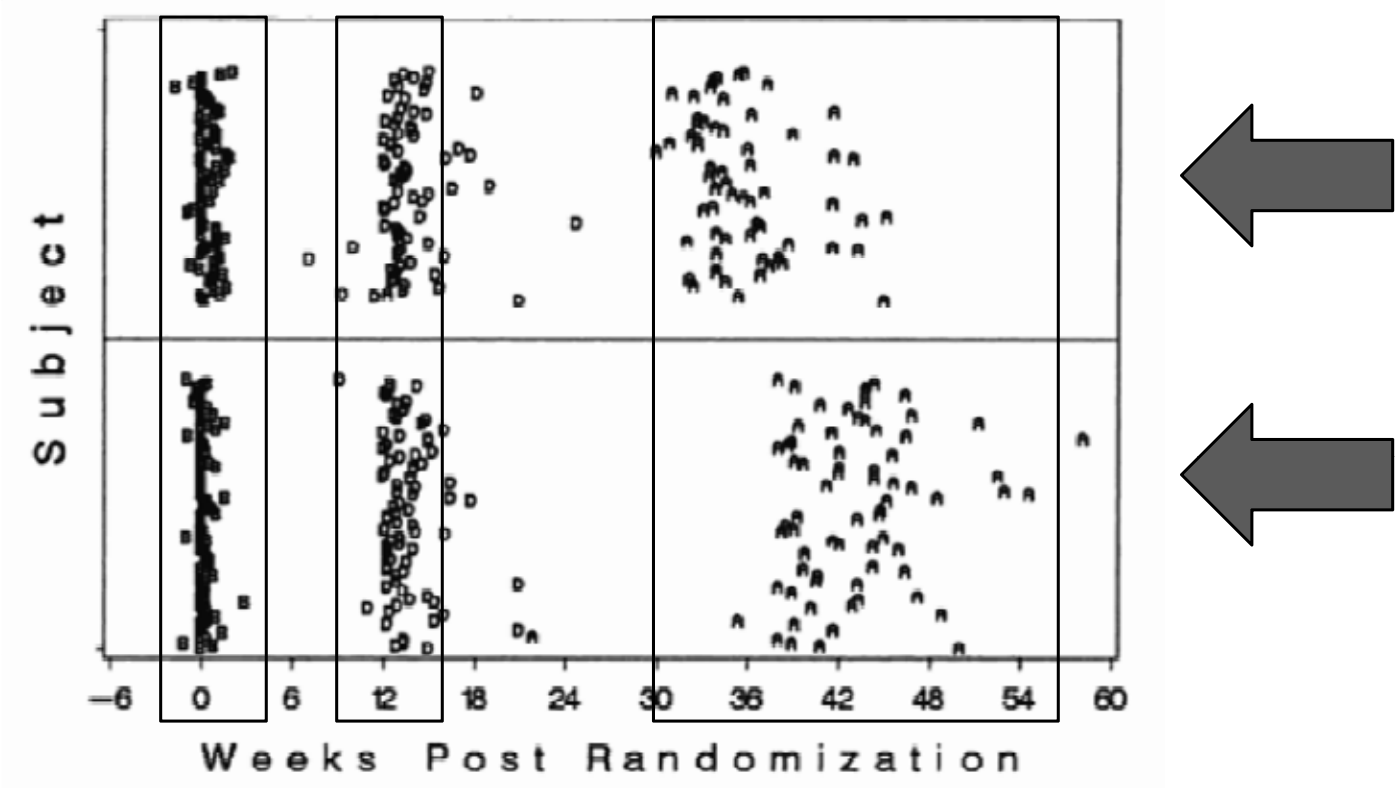


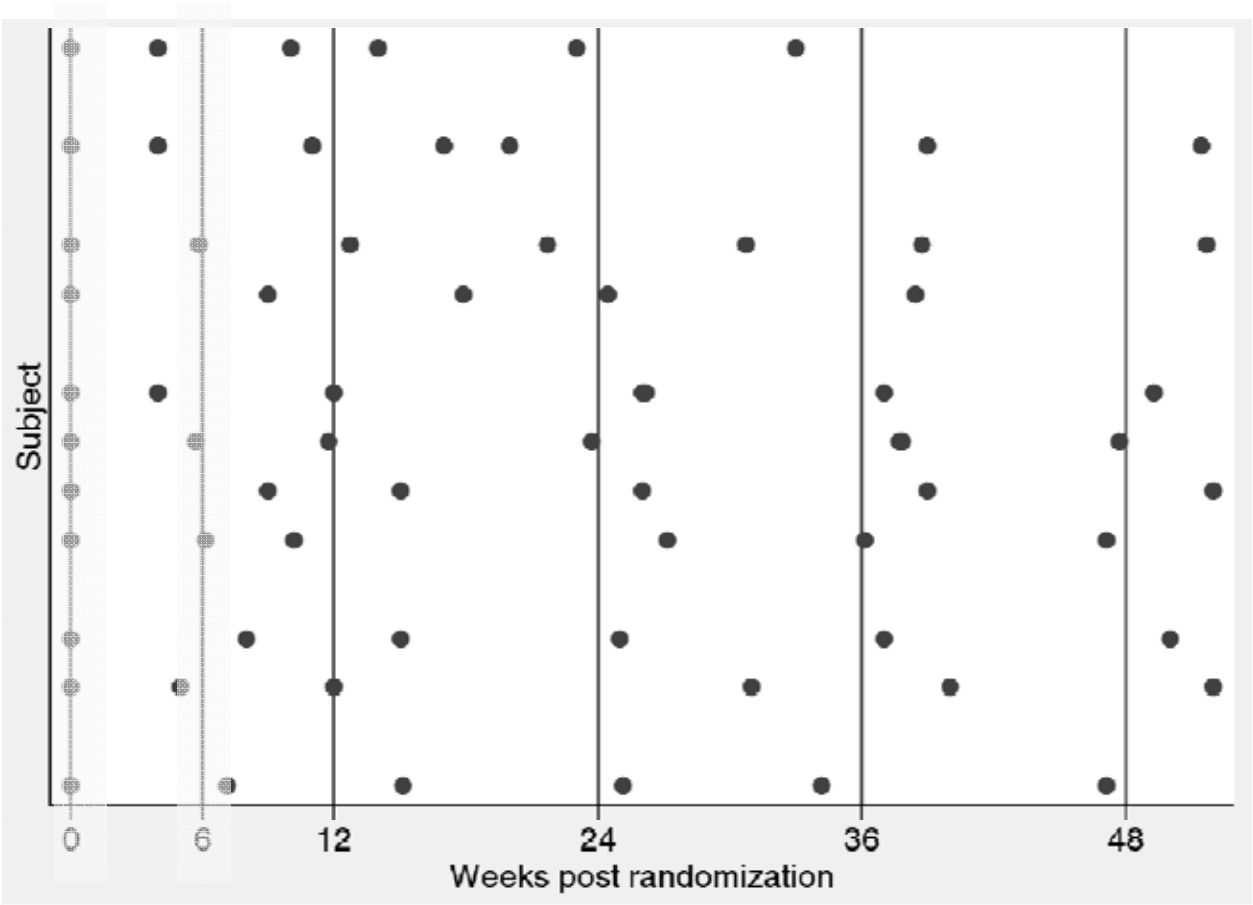
Figure 1.2. Timing of observations in a study with an event-driven design with assessments before (B), during (D), and 4 months after (A) therapy. Data are from the adjuvant breast cancer study [41]. Each row corresponds to a randomized subject. Subjects randomized to the 16-week regimen appear in the 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.* 2nd ed. Boca Raton, FL: Chapman and Hall/CRC Press; 2010.

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?

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

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

Level 1 model

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

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

Level 2 submodels

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

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

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

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

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 types of longitudinal studies and models
- Real-world example: Modeling the change in health-related quality of life (HRQoL)$_{in}$ patients with advanced HIV
  - OPTIMA

    Exploratory analysis
  - Models

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 was unclear.
- CSP #512, Options in Management with Antiretrovirals
- 2x2 open randomized study
  - 3 month therapy interruption vs. no interruption
  - Treatment intensification (5+ antiretroviral drugs) vs. standard treatment (4 or fewer drugs)
- UK, Canada, and US
- June 2001 - December 2007
- 368 patients randomized

Outcomes

- Primary and secondary outcomes
  - Time to first AIDS-defining event or death
  - Time to first serious adverse event
- No significant differences in outcomes among the management strategy groups

Outcomes (cont'd)

- Other sociodemographic and clinical data (e.g. age, sex, serious adverse events)
- Health-Related Quality of Life (HRQoL)
  - Baseline, 6, 12, 24, every 12 weeks thereafter
  - Health Utilities Index Mark 3 (HUI3)
  - 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
- 17 questions, 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

Research Questions

- What is the longitudinal effect of treatment intensification on HRQoL in patients with advanced HIV?
- What is the effect of ongoing serious adverse events (a time-dependent predictor) on HRQoL?

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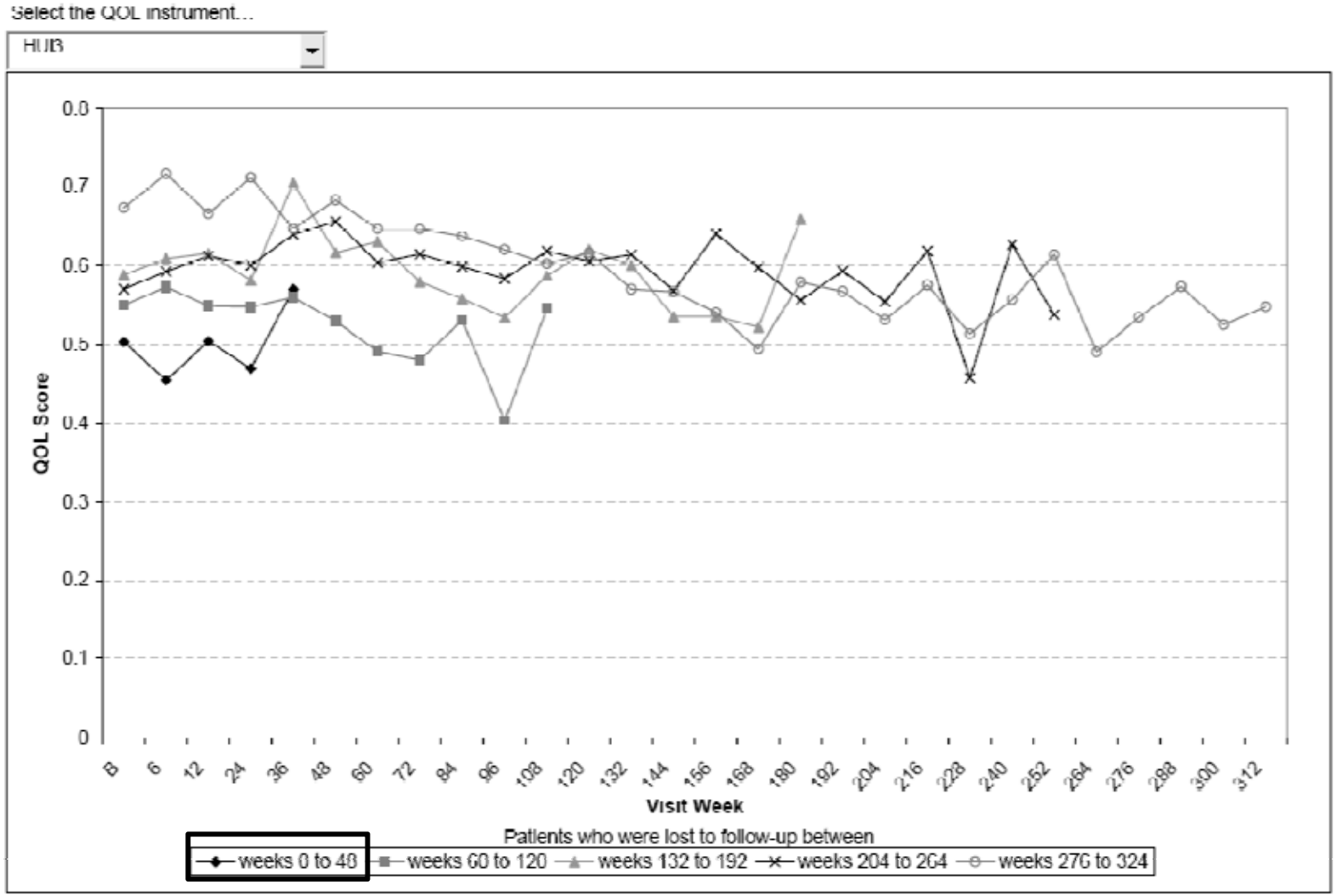
Missing Data

- 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 2010, Ch. 9, Multiple Imputation

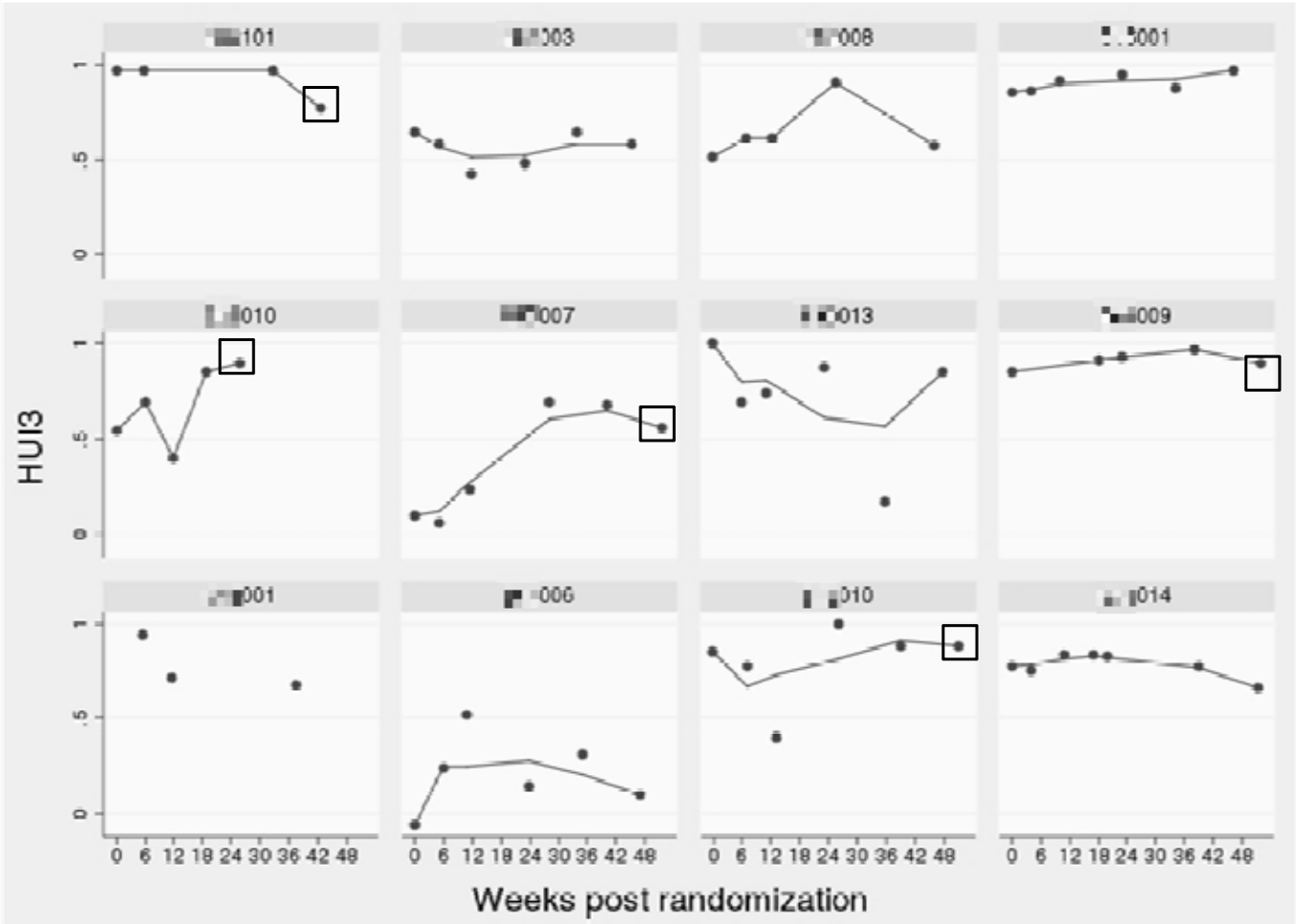
Excerpt from person-period OPTIMA HRQoL dataset

	Subject ID	Health Utilities Index	Indicator Treatment Intensification	Time in Years	Indicator ongoing SAE
4970	[illegible]003	0.85434496	0	0	0
4971	[illegible]003	0.97258	0	0.0958247775	0
4972	[illegible]003	0.85434496	0	0.2298794661	0
4973	[illegible]003	0.905401	0	0.5941136208	0
4974	[illegible]003	0.97258	0	0.7665982204	0
4975	[illegible]003	0.97258	0	0.9965776865	0
4976	[illegible]003	0.97258	0	1.2533356605	0
4977	[illegible]003	0.838222	0	1.4373716632	0
4978	[illegible]003	0.97258	0	1.6865160849	0
4979	[illegible]003	0.97258	0	1.8590006845	0
4980	[illegible]003	0.879352	0	2.2614647502	0
4981	[illegible]003	0.93145	0	2.7405886379	0
4982	[illegible]003	0.97258	0	2.9897330595	0
4983	[illegible]003	0.97258	0	3.2580424367	0
4984	[illegible]003	.	0	3.4688569473	0
4985	[illegible]003	0.9188368	0	3.5071868583	0
4986	[illegible]003	1	0	3.832991102	0
4987	[illegible]003	0.97258	0	4.1587953457	0
4988	[illegible]003	0.93145	0	4.5037645448	0
4989	[illegible]003	0.8530288	0	4.772073322	0
4990	[illegible]003	0.97258	0	5.2320328542	0
4991	[illegible]004	0.97258	1	0	0
4992	[illegible]004	0.97258	1	0.1533196441	0
4993	[illegible]004	0.85434496	1	0.2874743326	0
4994	[illegible]004	0.9188368	1	0.4791238877	1
4995	[illegible]004	0.838222	1	0.7091033539	1
4996	[illegible]004	1	1	0.9582477755	1
4997	[illegible]004	0.94516	1	1.1882272416	1
4998	[illegible]004	0.68467	1	1.3607118412	1

- Each subject has multiple records, one per assessment

Level 1: Within-Person Change over Time

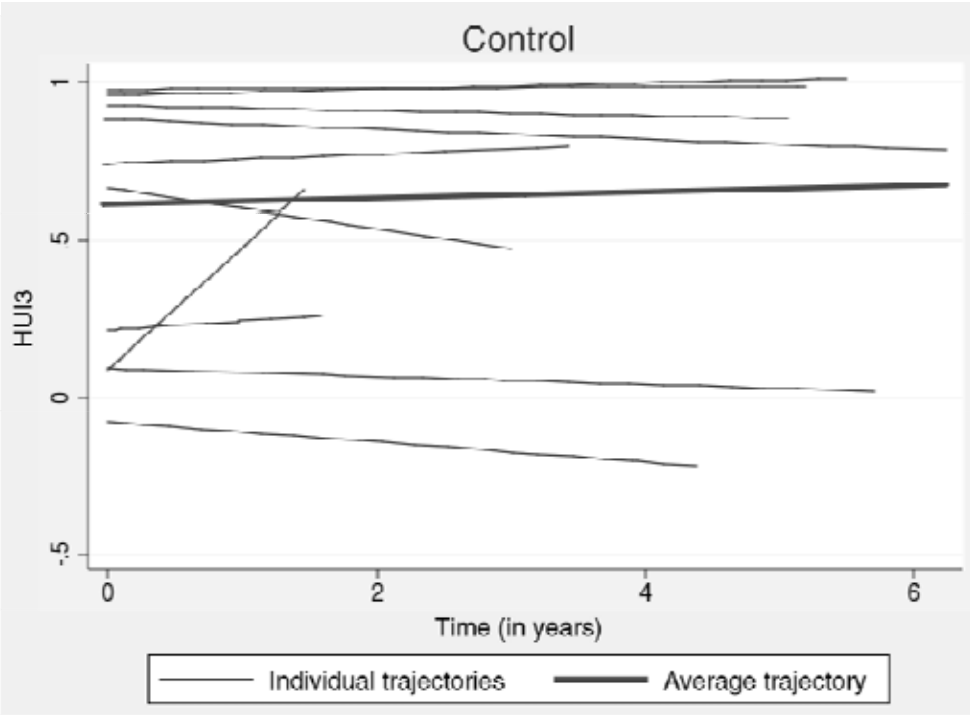
$$Y_{ij} = \left[\pi_{0i} + \pi_{1i}(time_{ij})\right] + \left[\varepsilon_{ij}\right]$$ Level 1 model

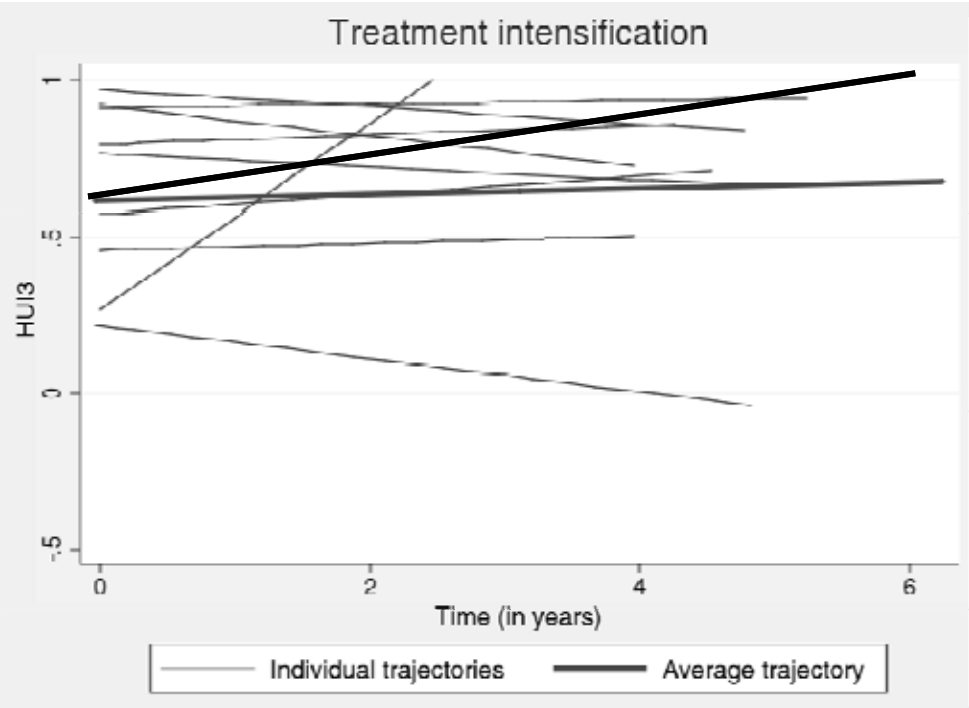


Level 2: Differences in Change Across People

$$\pi_{0i} = \gamma_{00} + \gamma_{01} INTVN + \zeta_{0i}$$
$$\pi_{1i} = \gamma_{10} + \gamma_{11} INTVN + \zeta_{1i}$$

Level 2 submodels





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Research Questions

- What is the longitudinal effect of treatment intensification on HRQoL in patients with advanced HIV?
- What is the effect of ongoing serious adverse events (a time-dependent predictor) on HRQoL?

Model for longitudinal treatment effect

- What is the longitudinal effect of treatment intensification on HRQoL in patients with advanced HIV?

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

$$HUI3_{ij} = \left[(\gamma_{00} + \gamma_{10}TIME_{ij} + \gamma_{01}INTENSIFY_i + \gamma_{11}(INTENSIFY_i \times TIME_{ij})\right] + \left[\zeta_{0i} + \zeta_{1i}TIME_{ij} + \varepsilon_{ij}\right]$$

```
proc mixed data = qol;

model hui3 =
time_years
intensify
time_years*intensify
/ solution ddfm=kr;

random int time_years /
subject=id
type=un;

run;
```

```
/*1. Evokes mixed procedure, identifies dataset, specifies */
/*   default estimation method or restrict max likelihood*/
/*2. Dependent variable, QOL instrument HUI3*/
/*3. Time in years*/
/*4. Intensification group indicator*/
/*5. Interaction term, time in years*intensification*/
/*6. Significance tests for all fixed effects and Kenward-*/
/*   Roger method of degrees of freedom*/
/*7. Specifies the intercept and time as random effects*/
/*8. Specifies observations as nested within ID*/
/*9. Specifies an unstructured variance/covariance matrix*/
/*   for the random effects*/
```

Results

The Mixed Procedure

Covariance Parameter Estimates

Cov Parm	Subject	Estimate	Error	Value	Pr Z	
UN(1,1)	id	0.07349	0.006017	12.21	0001	/* Variance estimate for intercept*/
UN(2,1)	id	-0.00416	0.001222	-3.41	0.0007	/* Covariance estimate for intercept and slope*/
UN(2,2)	id	0.002837	0.000427	6.64 <.	<.0001	/* Variance estimate for slope*/
Residual		0.02942	0.000653	45.08	<.0001	/* Level 1 residual*/

Fit Statistics

-2 Res Log Likelihood	-1753.4
AIC (smaller is better)	-1745.4
AICC (smaller is better)	-1745.3
BIC (smaller is better)	-1729.7

Results (cont'd)

$$HUI3_{ij} = \left[(\gamma_{00} + \gamma_{10}TIME_{ij} + \gamma_{01}INTENSIFY_i + \gamma_{11}(INTENSIFY_i \times TIME_{ij})\right] + \left[\zeta_{0i} + \zeta_{1i}TIME_{ij} + \varepsilon_{ij}\right]$$

Solution for Fixed Effects

Effect	Estimate	Standard Error	DF	t Value	Pr > |t|	
Intercept	0.5967	0.02056	358	29.02	<.0001	/* γ_{00} */
time_years	-0.01005	0.005510	191	-1.82	0.0696	/* γ_{10} */
intensify	0.03245	0.02970	359	1.09	0.2754	/* γ_{01} */
time_years*intensify	-0.00348	0.007979	188	-0.44	0.6634	/* γ_{11} */

Conclusions:
- no sustained differences in HUI3 HRQoL scores between the 2 groups and over time

Research Questions

- What is the longitudinal effect of treatment intensification on HRQoL in patients with advanced HIV?
- What is the effect of ongoing serious adverse events (a time-dependent predictor) on HRQoL?

Model for effect of ongo ing serious adverse events (SAE)

- What is the effect of ongoing serious adverse events on HRQoL?

$$HUI3_{ij} = \left[(\gamma_{00} + \gamma_{10}TIME_{ij} + \boxed{\gamma_{20}SAE_{ij}} + (\boxed{\gamma_{30}SAE_{ij} \times TIME_{ij}})\right] + \left[\zeta_{0i} + \zeta_{1i}TIME_{ij} + \varepsilon_{ij}\right]$$

```
proc mixed data = qol;          /*1. Evokes mixed procedure, identifies dataset, specifies */
                                /*   default estimation method or restrict max likelihood*/
model hui3 =                    /*2. Dependent variable, QOL instrument HUI3*/
time years                      /*3. Time in years*/
sae_ongoing                     /*4. Indicator ongoing serious adverse event (SAE)*/
time_years*sae_ongoing          /*5. Interaction term, time in years*SAE*/
/ solution ddfm=kr;             /*6. Significance tests for all fixed effects and Kenward-*/
                                /*   Roger method of degrees of freedom*/
random int time_years /         /*7. Specifies the intercept and time as random effects*/
subject=id                      /*8. Specifies observations as nested within ID*/
type=un;                        /*9. Specifies an unstructured variance/covariance matrix*/
                                /*   for the random effects*/
run;
```

Results

$$HUI3_{ij} = \left[(\gamma_{00} + \gamma_{10}TIME_{ij} + \gamma_{20}SAE_{ij} + (\gamma_{30}SAE_{ij} \times TIME_{ij})\right] + \left[\zeta_{0i} + \zeta_{1i}TIME_{ij} + \varepsilon_{ij}\right]$$

Solution for Fixed Effects

Effect	Estimate	Standard Error	DF	t Value	Pr > |t|	
Intercept	0.6130	0.01483	363	41.32	<.0001	/* γ_{00} */
time_years	-0.00922	0.003879	192		0.0185	/* γ_{10} */
sae_ongoing	-0.03967	0.02604	4575	-2.38	0.1278	/* γ_{20} */
time_year*sae_ongoin	-0.03445	0.01116	4429	-3.09	0.0020	/* γ_{30} */

-1.52

Conclusions:
- Effect of ongoing SAE status varies over time
- Rate of change in HUI3 scores over time differs by ongoing SAE status

-.009/year (no ongoing SAEs)

vs.

-.04/year (ongoing SAEs; -0.00922+ -0.03445)

A few final notes

- Centering
  - Simplifies interpretation
  - 2x2 trial?
    - Treatment A, Treatment B, Both
    - 0.5 = patient randomized to the group
    - -0.5 = patient not randomized to the group
    - Ex. Randomized to both? A=.5; B=.5; AB=.25

A few final notes (cont'd)

- Model fit
  - Deviance statistic (-2 Res Log Likelihood)
    - Models must be estimated using identical data
    - Models must be nested within one another
  - Akaike Information Criteria (AIC)/Bayesian Information Criteria (BIC)
    - Models must be fit to the identical set of data; not-nested O K
    - Smaller information criterion is better
    - Raftery (1995) on BIC
      - 0-2 "weak"
      - 2-6 "positive"
      - 6-10 "strong"
      - >10 "very strong"

Summary

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

Suggested References

- Fairclough DL. *Design and Analysis of Quality of Life Studies in Clinical Trials*. 2nd ed. Boca Raton, FL: Chapman and Hall/CRC Press; 2010.

- 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?

- Budget Impact Analysis– 11/28/12
  - Register: http://www.hsrd.research.va.gov/cyberseminars/catalog-upcoming-series.cfm?seriessort=hcea

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