Longitudinal Data Analysis

By: Jennifer Le-Rademacher, PhD, Assistant Professor
Medical College of Wisconsin, Division of Biostatistics

Friday, December 6th, 2013
12:00-1:00 pm

The Medical College of Wisconsin is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

The Medical College of Wisconsin designates this live activity for a maximum of 1.0 *AMA PRA Category 1 Credit™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Hours of Participation for Allied Health Professionals

The Medical College of Wisconsin designates this activity for up to 1.0 hours of participation for continuing education for allied health professionals.

Educational Objectives

- Define longitudinal data
- Longitudinal studies vs. cross-sectional studies
- Analysis methods for longitudinal data
- Missing data mechanism
- Considerations for design and analysis of longitudinal studies

Financial Disclosure

- In accordance with the ACCME® standard for Commercial Support Number 6, all in control of content disclosed any relevant financial relationships. The following in control of content had **no** relevant financial relationships to disclose.

Name:	Role in Meeting:
Kwang Woo Ahn, PhD	Activity Director
Haley Montsma, BBA	Planning Committee
Jennifer Le-Rademacher, PhD	Presenter

Evaluation Forms

Your opinion matters!

Help us plan future meetings, by completing and submitting your evaluation forms.

Thank you.

Longitudinal Data

- A type of repeated measures
- Outcomes are measured at multiple time points for each subject
  - Same number of time points per subject (equally spaced)
  - Under the same or different conditions
- Allows study of change overtime
- Outcome measures can be quantitative or qualitative

Longitudinal Data Example

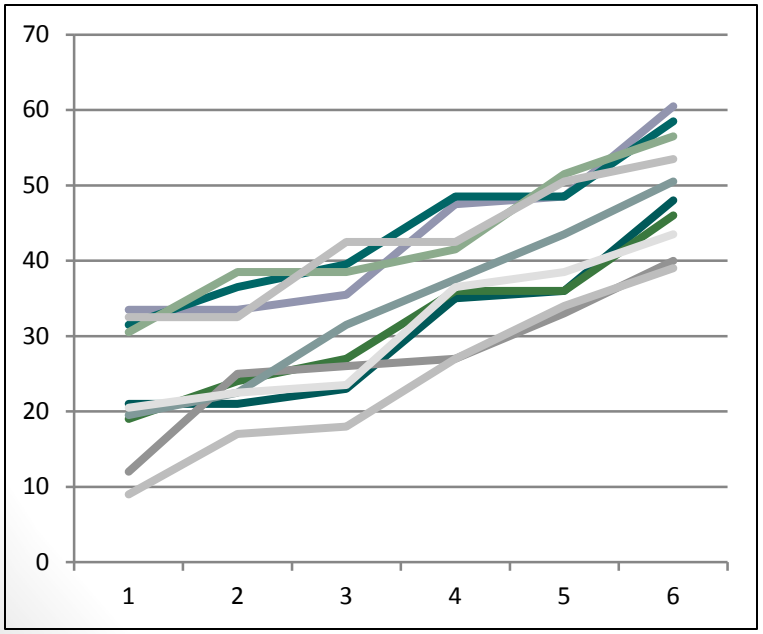
Patient ID	Treatment	Age	Gender	Race	Response			
					Enrollment	1 m	2 m	3 m
1	Control	25	Male	1	11	43	45	30
2	Control	18	Male	0	20	15	27	39
3	Control	46	Female	0	0	12	0	9
4	Control	21	Male	1	21	21	21	35
…	…	…	…	…	…	…	…	…
97	Active	63	Female	1	25	41	50	15
98	Active	25	Male	0	45	28	32	24
99	Active	30	Male	1	16	23	119	40
100	Active	23	Female	0	21	9	12	15

Longitudinal Study vs. Cross-sectional Study

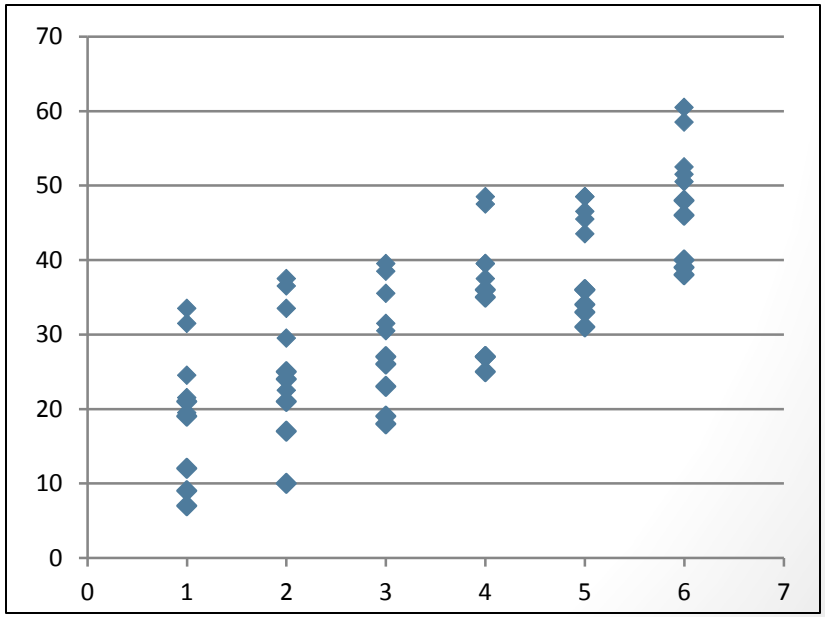
- Advantages:
  - Allows study of change over time
  - Adjusts for variability between individuals
  - Needs fewer subjects
- Disadvantages:
  - Longer follow-up time
  - Missing data
  - Complex design and analysis

Example: Longitudinal vs. Cross-sectional

- Follow each child from one to six years of age (n = 10)
- Follow pattern of growth
- Adjust for individual differences at baseline



- Measure each child once need 10 children at each age level (n = 60)
- No pattern of growth
- Adjustment for differences at baseline not possible



Longitudinal Study - Designs

- Prospective randomized or observational studies
  - Follow patients from enrollment to end of study
  - Better data quality
    - Selection of time-points
    - Follow-up mechanism
- Retrospective studies
  - Collect data at various time points in the past
  - Missing data can be a major problem
    - Depends on data availability
    - No follow-up mechanism in place

Analysis Considerations

- Study objectives drive design and analysis
- Multiple methods available
  - Need to select appropriate method for study
- Account for correlation between measurements from the same subject
  - Ignore correlation may lead to incorrect inferences, bias results, or less precise estimates
  - Pattern of correlation may depend on time lag
- Presence of missing data
  - Ignore missing may lead to incorrect conclusions

Analysis Example

- A clinical trial was conducted to evaluate the effect of a meditation technique on children's ability to stay focus: 352 children were randomized to either practice this meditation technique (n = 170 (48%)) or continue their current activity (n = 182 (52%)).
- Response: number of consecutive minutes stay focused on a task.
- Response was measured at
  - Time of randomization
  - 1, 2, 3, and 4 months of practice

Example:
Summary Statistics

Time Point	Active		Control	
	Mean (SD)	Median (min – max)	Mean (SD)	Median (min – max)
Randomization	14.9 (13.1)	10 (0 – 50)	14.9 (13.1)	10 (0 – 50)
1 month	24.5 (13.3)	30 (0 – 50)	16.5 (13.0)	20 (0 – 50)
2 months	23.3 (10.4)	20 (0 – 50)	17.1 (12.2)	20 (0 – 50)
3 months	20.7 (12.2)	10 (0 – 50)	15.0 (12.3)	10 (0 – 50)
4 months	19.1 (13.0)	10 (0 – 50)	15.3 (13.4)	10 (0 – 50)

- Similar duration of focus at randomization
- Active treatment group:
  - Response increased after randomization
  - Slightly decreased after 1st month
- Control group:
  - No increase in response after randomization

Analysis Approaches

1. Repeated (separate) analyses
   - Response at each time point
   - Mean response over all (or a few selected) time points
   - Response change between time points
2. Transition models
   - Model effect conditional on history of past responses
3. Multivariate analysis (MANOVA)
4. Marginal models – population average effect
5. Conditional models - conditional effect
   - Mixed models

Analysis Approaches

1. Repeated (separate) analyses
   - Response at each time point
   - Mean response over all (or a few selected) time points
   - Response change between time points
2. Transition models
   - Model effect conditional on history of past responses
3. Multivariate analysis (MANOVA)
4. Marginal models - population average effect
5. Conditional models - conditional effect
   - Mixed models

Example:
Separate analyses at each time point

Time Point	Active vs. Control	
	Estimate (95% CI)	P-value
Randomization	0.05 (-2.69, 2.79)	0.97
1 month	7.99 (5.23, 10.75)	< .0001
2 months	6.15 (3.77, 8.53)	< .0001
3 months	5.71 (3.13, 8.28)	< .0001
4 months	3.78 (1.01, 6.56)	0.0076

- No difference in duration of focus between treatment groups at time of randomization
- At each time point post randomization, active treatment was strongly associated with longer duration of focus
- Largest effect at 1 month (~ 8 mins) and smallest effect at 4 months (~4 mins)
- No comparison of responses between time points

Example:
Analysis of mean response

Mean response over 4 post-randomization time points	Parameter Estimates (95% Confidence interval)	P-value
Intercept	7.41 (6.18, 8.64)	<.0001
Baseline	0.36 (0.31, 0.41)	<.0001
Active	4.71 (3.34, 6.07)	<.0001

- Initial duration of focus was highly associated with mean duration of focus post randomization.
- After adjusting for initial duration of focus (baseline), the average concentration time over all time points post randomization was higher in the active treatment group compared to the control group.
- Give estimate of average effect over all post randomization time points, no comparison between time points.

Example: Analysis at each time point adjusting for baseline

	Parameter	1 m	2 m	3 m	4 m
Change from baseline	Intercept	1.59 (0.13)	2.25 (0.02)	0.11 (0.91)	0.38 (0.70)
	Active	7.94 (<.001)	6.10 (<.001)	5.65 (<.001)	3.73 (0.01)
Focus duration	Intercept	10.24 (<.001)	10.92 (<.001)	7.69 (<.001)	8.20 (<.001)
	Baseline	0.42 (<.001)	0.42 (<.001)	0.49 (<.001)	0.47 (<.001)
	Active	7.97 (<.001)	6.13 (<.001)	5.68 (<.001)	3.76 (<.001)

- Baseline can be adjusted as a change in response or as a covariate in the model.
- Inclusion as covariate allows estimation of the effect of baseline measure on response at other time points
- Give cumulative effect from baseline, no comparison between post randomization time points

Analysis Approaches

1. Repeated (separate) analyses
   - Do not use all information
   - Lack of comprehensive picture of change overtime
   - Baseline measure can be included as change in response from baseline or as a covariate in analysis
   - Only well-defined with equal number of measurements per subject (with missing data, analyses may include different sets of subjects).
   - Assume covariates are the same for all observations in one subject, i.e., no time-varying covariates

Example: Transition Models

Outcome	Parameter	1 m	2 m	3 m	4 m
Focus duration	Intercept	10.24 (<.001)	9.67 (<.001)	4.20 (<.001)	5.40 (<.001)
	Prior response	0.42 (<.001)	0.45 (<.001)	0.63 (<.001)	0.66 (<.001)
	Active	7.97 (<.001)	2.53 (0.02)	1.83 (0.10)	0.03 (0.98)

- Response between consecutive time points are highly correlated
- Given the same initial duration of focus, focus time in the active treatment group was significantly higher than that of the control group.
- Given the same response at one month post randomization, focus duration in the active treatment group was ~ 2.5 mins longer than the control group.
- Given the same focus duration in the immediate prior response, there was no improvement in focus time in the active group compared to the control group.

Analysis Approaches

2. Transition models
   - Require equal number of measurements
   - Meaningful with equally-spaced measures
   - Conditional interpretation
   - Overall effect can not be determined from model

Example: Linear Mixed Models

Overall Tests of Fixed Effects

Effect	Num DF	Den DF	F value	P-value
Baseline	1	349	183.55	<.0001
Active	1	349	45.98	<.0001
Time	3	1050	13.01	<.0001
Active*Time	3	1050	3.49	0.0152

Treatment Effect

Time Point	Estimate (95% CI)	P-value
1 month	7.96 (5.65, 10.28)	<.0001
2 months	6.13 (3.81, 8.44)	<.0001
3 months	5.68 (3.37, 8.00)	<.0001
4 months	3.76 (1.45, 6.08)	0.0015

- Model the effect of time and treatment as well as interaction between time and treatment
- Treatment effect similar to the analysis shown on slide 18

Example: Linear Mixed Models

Time Effect

Time Comparison	Estimate (95% CI)	P-value
Control		
2 m vs. 1 m	0.66 (-1.12, 2.44)	0.47
3 m vs. 1 m	-1.48 (-3.26, 0.30)	0.10
4 m vs. 1 m	-1.21 (-2.99, 0.57)	0.18
3 m vs. 2 m	-2.14 (-3.92, -0.36)	0.02
4 m vs. 3 m	0.27 (-1.51, 2.06)	0.76
Active		
2 m vs. 1 m	-0.26 (-1.12, 2.44)	0.69
3 m vs. 1 m	-2.62 (-3.26, 0.30)	<.0001
4 m vs. 1 m	-3.31 (-2.99, 0.57)	<.0001
3 m vs. 2 m	-2.37 (-3.65, -1.08)	0.0003
4 m vs. 3 m	-0.69 (-1.97, 0.60)	0.29

Analysis Approaches

4. Marginal models
   - Flexible model
   - Can handle unbalanced data
   - Assume missing completely at random assumption
5. Mixed models – random effects
   - Flexible model
   - Can handle unbalanced data
   - Assume missing at random assumption

Missing Data

Missing Data

- A common problem in longitudinal studies
  - Subjects may drop out for various reasons
  - Can bias conclusions drawn from study
- Important design consideration: try to minimize missing data
- Missing data mechanism
  - Missing completely at random
  - Missing at random
  - Missing not at random

Missing Values

- Intermittent missing values
  - Patients have missing response at follow-up j but the response is observed at time $k > j$.
  - Difficult to model or explore pattern of intermittent missing values due to number of combinations.
  - May be able to recover missing information.
- Dropouts
  - Missing response at follow-up time j leads to missing data for all time points $k > j$.
  - Can explore dropout patterns to understand mechanism.

Missing Completely at Random

- The reason for missing is completely unrelated to response
  - Example: Patients moved out of area
- Assume subjects with complete data are a random sample of population
- The strongest assumption about missing data
- Not realistic in most situations
- Analysis using complete cases are valid under this assumption
  - Separate repeated analysis
  - Transition models
  - MANOVA
  - Marginal models

Missing at Random

- The reason for missing can be related to previously observed responses but not related to missing responses
  - Example: Patients whose response falls below a predefined value will be not be followed up further in the study.
- A more relaxed assumption about missing data
- Analysis excluding cases with missing data are invalid under this assumption
- Analysis using likelihood approaches provides valid inferences
  - Mixed models

Exploring Missing Mechanism

- Identify covariates associated with dropout (regression model)
- Identify association between dropout and observed response
  - Plot of response by dropout time
  - Regression model

Solutions for Data Missing (Completely) at Random

- Complete-case analysis
  - Not recommended unless missing completely at random or interest is only on completers
- Imputation:
  - Single imputation - Not recommended in most cases
    - Last observation carried forward
      - Exact value
    - Mean value
    - Extrapolated value
  - Multiple imputation
- Weight regression
- Mixed models

Conclusions

- Longitudinal studies allow evaluation of change over time
- Design requires careful considerations to ensure data quality
  - Number of time points to evaluate outcomes
  - Follow-up procedure
- Analysis and interpretation
  - Various methods available
  - Appropriate analysis depends on study objectives and design
  - Analysis is complex especially in the presence of
    - Missing data
    - Categorical response
    - Time-varying covariates

Conclusions

Consult the Biostatistics Consulting Service if you plan to conduct a longitudinal study

- To schedule a meeting contact: Haley Montsma at (414) 955-7439 or hmontsma@mcw.edu
- Website: **www.mcw.edu/biostatsconsult.htm**

Free Drop-in Consulting

- **Medical College of Wisconsin**:
  Tuesdays and Thursdays
  Time: 1:00 PM—3:00 PM
  Building: Health Research Center
  Room: H2400 Biostatistics

- **MCW Cancer Center**
  Wednesdays 10:00 AM—12:00 PM
  Fridays 1:00 PM—3:00 PM
  Building: MCW Clinical Cancer Center
  Room: Clinical Trials Support Room
  CLCC: 3236 (Enter through C3233)

- **Froedtert Pavilion**:
  Mondays & Wednesdays
  Time: 1:00 PM—3:00 PM
  Building: Froedtert Pavilion
  Room: TRU Conference Room L742

- **Clement J. Zablocki VA Medical Center:**
  1st & 3rd Monday of the month
  Time: 9:00 AM—11:00 AM
  Building: 111, 5th Floor B-wing
  Room: 5423

- **Marquette University:**
  Every Tuesday
  Time: 8:30 AM—10:30 AM
  Building: School of Nursing, Clark Hall
  Room: Office of Research and Scholarship: 112D
  Contact: **Jessica Pruszynski, PhD** to make an appointment
  Please note: Priority given to MU Nursing and Dental School personnel

Questions?