Advanced Topics In SMART Design and Data Analysis, Part 1

Module 5
General Objectives

• A taste of how data from a SMART can be analyzed to address various scientific questions
  o How to frame scientific questions
  o Experimental cells to be compared
  o Resources you can use for data analysis
  o Less details, more focus on making you feel comfortable with the general approach.
Outline

• Brief review of using end-of-study outcome to compare embedded AIs

• Learn how to use repeated outcome measures from a SMART to compare embedded AIs

• Review three types of scientific questions you can answer with repeated outcome measures
  o Difference in end-of-study outcome
  o Difference in Area Under the Curve (AUC)
  o Delayed effects

• Sample size considerations for planning SMARTs to compared embedded AIs with repeated outcome measures
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• Brief review of using end-of-study outcome to compare embedded AIs

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• Sample size considerations for planning SMARTs to compare embedded AIs with repeated outcome measures
For simplicity assume response status was assessed at one time point (week 8)
ADHD SMART
PI: Pelham

4 embedded adaptive interventions

**AI #1:**
Start with MED;
if non-responder AUGMENT, else CONTINUE

**AI #2:**
Start with BMOD;
if non-responder AUGMENT, else CONTINUE

**AI #3:**
Start with MED;
if non-responder INTENSIFY, else CONTINUE

**AI #4:**
Start with BMOD;
if non-responder INTENSIFY, else CONTINUE
Recall Typical Primary Aim 3

Compare 2 embedded AIs

**AI #1:**
Start with MED;
if non-responder AUGMENT,
else CONTINUE

**AI #2:**
Start with BMOD;
if non-responder AUGMENT,
else CONTINUE
Comparison of Subgroups A+B vs. D+E
End of Study Primary Outcome Analysis Review

Step 1: Weight and replicate the data

Weighting
- Accounts for over/underrepresentation of responders or non-responders
- Because of the randomization scheme

Replicating
- Allows us to use standard software to do simultaneous estimation and comparison
- Because participants are consistent with more than one AI
End of Study Primary Outcome Analysis Review

Step 2: Select and fit a model, such as

\[ E[Y|A_1, A_2] = \beta_0 + \beta_1 A_1 + \beta_2 A_2 + \beta_3 A_1 A_2 \]
Step 3: Estimate linear combinations of parameters to compare AI #1 and AI #2

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$E[Y|A_1, A_2] = \beta_0 + \beta_1 A_1 + \beta_2 A_2 + \beta_3 A_1 A_2$
Step 3: Estimate linear combinations of parameters to compare AI #1 and AI #2

\[ E[Y|A_1, A_2] = \beta_0 + \beta_1 A_1 + \beta_2 A_2 + \beta_3 A_1 A_2 \]

Mean Y under (MED, AUG) = \( \beta_0 + \beta_1(-1) + \beta_2(-1) + \beta_3(-1)(-1) \)
Step 3: Estimate linear combinations of parameters to compare AI #1 and AI #2

$$E[Y|A_1, A_2] = \beta_0 + \beta_1 A_1 + \beta_2 A_2 + \beta_3 A_1 A_2$$

Mean Y under (MED, AUG) = \(\beta_0 + \beta_1(-1) + \beta_2(-1) + \beta_3(-1)(-1)\)

Mean Y under (BMOD, AUG) = \(\beta_0 + \beta_1(1) + \beta_2(-1) + \beta_3(1)(-1)\)
End of Study Primary Outcome Analysis Review

Step 3: Estimate linear combinations of parameters to compare AI #1 and AI #2

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$E[Y|A_1, A_2] = \beta_0 + \beta_1 A_1 + \beta_2 A_2 + \beta_3 A_1 A_2$

The difference between $(MED, AUG)$ and $(BMOD, AUG)$:

$(\beta_0 - \beta_1 - \beta_2 + \beta_3) - (\beta_0 + \beta_1 - \beta_2 - \beta_3) = -2\beta_1 + 2\beta_3$
Outline

• Brief review of using end-of-study outcome to compare embedded AIs

• **Learn how to use repeated outcome measures from a SMART to compare embedded AIs**

• Review three types of scientific questions you can answer with repeated outcome measures
  o Difference in end-of-study outcome
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  o Delayed effects

• Sample size considerations for planning SMARTs to compare embedded AIs with repeated outcome measures
Repeated Outcome Measures From SMART

First-stage intervention

Response

MED

Non-Response

BMOD

Intermediate outcome

Response

Week 8

Beginning of school year Y1

A1

Y2 / R Status

End of school year Y3

Second-stage intervention

Continue

Augment

Intensify

Experimental Conditions

Subgroups

A

B

C

D

E

F

Non-Response

R

R

R
Longitudinal Outcome Analysis

Step #1: Weight and replicate the person-period data

**Weighting**
- Accounts for over/underrepresentation of responders or non-responders
- Because of the randomization scheme

**Replicating**
- Allows us to use standard software to do simultaneous estimation and comparison
- Because participants are consistent with more than one AI
Longitudinal Outcome Analysis

**Step #1:** Weight and replicate the person-period data

Fake data would look like this:

<table>
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<tr>
<th>ID</th>
<th>Month</th>
<th>ODD at baseline</th>
<th>Response Status</th>
<th>School Perf</th>
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Longitudinal Outcome Analysis

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Longitudinal Outcome Analysis

Step #2: Select and fit a model

\[ E[Y|A_1, A_2] = \beta_0 + \beta_1 A_1 + \beta_2 A_2 + \beta_3 A_1 A_2 \]

- This model is for a single end-of-study outcome
- But we can extend for additional repeated outcome measures
Longitudinal Outcome Analysis

**Step #2**: Select and fit a model for the repeated outcome measurements

- The model we select should allow the outcome at each stage to be impacted only by intervention options that were offered prior to that stage.

```
Beginning of school year  | Week 8  | End of school year
Y1  A1  Y2 / R Status  A2  Y3
```
Longitudinal Outcome Analysis

**Step #2:** Select and fit a model for the repeated outcome measurements

- The model we select should allow the outcome at each stage to be impacted only by intervention options that were offered prior to that stage.
Longitudinal Outcome Analysis

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Longitudinal Outcome Analysis

Step #2: Select and fit a model for the repeated outcome measurements

- The model we select should allow the outcome at each stage to be impacted only by intervention options that were offered prior to that stage.

- Failing to properly account for the ordering of the measurement occasions relative to the intervention options can lead to bias (see Lu et al., 2016).
Longitudinal Outcome Analysis

Step #2: Select and fit a model for the repeated outcome measurements

- Piecewise (segmented) linear regression models can be useful in this setting.
Longitudinal Outcome Analysis

Step #2: Select and fit a model for the repeated outcome measurements

- Piecewise (segmented) linear regression models can be useful in this setting.
- What is a piecewise linear regression?
Step #2: Select and fit a model for the repeated outcome measurements

- Piecewise (segmented) linear regression models can be useful in this setting.

- What is a piecewise linear regression?
  - It’s just a regression
  - Where you can fit a separate line for different intervals
  - The boundary for the time intervals can form a transition point.
Longitudinal Outcome Analysis

Step #2: Select and fit a model for the repeated outcome measurements

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Longitudinal Outcome Analysis

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Longitudinal Outcome Analysis

Step #2: Select and fit a model for the repeated outcome measurements

- Piecewise (segmented) linear regression models can be useful in this setting.

Interval 2: Second-stage intervention

Beginning of school year | Week 8 | End of school year

Y1  A1  Y2 / R Status  A2  Y3
Longitudinal Outcome Analysis

Step #2: Select and fit a model for the repeated outcome measurements

- Piecewise (segmented) linear regression models can be useful in this setting.

Transition point

Interval 1: First-stage intervention  
Interval 2: Second-stage intervention

Beginning of school year  |  Week 8  |  End of school year

Y1  |  A1  |  Y2 / R Status  |  A2  |  Y3
Longitudinal Outcome Analysis

Step #2: Select and fit a model for the repeated outcome measurements

• Piecewise (segmented) linear regression models can be useful in this setting.

• The linear trend in the outcome during the first stage can vary from second-stage and be impacted by different variables.
Longitudinal Outcome Analysis

Step #2: Select and fit a model

- To fit a separate line for each interval: meet $S_1$ and $S_2$
- $S_1$: indicator for the number of months spent so far in the first stage by time $t$,
- $S_2$: indicator for the number of months spent so far in the second stage by time $t$
Longitudinal Outcome Analysis

Step #2: Select and fit a model

- $S_1$: How many months spent so far in stage 1 by time $t$,
- $S_2$: How many months spent so far in stage 2 by time $t$

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Interval 1: First-stage intervention
Interval 2: Second-stage intervention

Beginning of school year | Week 8 | End of school year

Y1 | A1 | Y2 / R Status | A2 | Y3
Longitudinal Outcome Analysis

**Step #2: Select and fit a model**

- \( S_1 \): How many months spent so far in stage 1 by time \( t \),
- \( S_2 \): How many months spent so far in stage 2 by time \( t \)

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**Interval 1:** First-stage intervention

**Interval 2:** Second-stage intervention

- **Beginning of school year**
- **Week 8**
- **End of school year**

Longitudinal Outcome Analysis

Step #2: Select and fit a model

- $S_1$: How many months spent so far in stage 1 by time $t$,
- $S_2$: How many months spent so far in stage 2 by time $t$

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**Interval 1:** First-stage intervention

**Interval 2:** Second-stage intervention

Beginning of school year | Week 8 | End of school year

Y1 ——— A1 ——— Y2 / R Status ——— A2 ——— Y3
**Longitudinal Outcome Analysis**

**Step #2: Select and fit a model**

- $S_1$: How many months spent so far in stage 1 by time $t$,
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**Interval 1:** First-stage intervention

**Interval 2:** Second-stage intervention

Beginning of school year  | Week 8  | End of school year

Y1  | A1  | Y2 / R Status  | A2  | Y3
Longitudinal Outcome Analysis

**Step #2: Select and fit a model**

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Longitudinal Outcome Analysis

Step #2: Select and fit a model

• Let’s ignore treatment assignment for now
• i.e., imagine everyone is on the same adaptive intervention

\[ E[Y_t] = \beta_0 + \beta_1 S_1 + \beta_2 S_2 \]
Longitudinal Outcome Analysis

**Step #2: Select and fit a model**

\[
E[Y_t] = \beta_0 + \beta_1 S_1 + \beta_2 S_2
\]

\(\beta_0\): Expected SP at beginning of school year

\(\beta_1\): Stage 1 slope: *Expected monthly change in SP during stage 1*

\(\beta_2\): Stage 2 slope: *Expected monthly change in SP during stage 2*
Longitudinal Outcome Analysis

Step #2: Select and fit a model

- Now, let’s incorporate the treatment assignment in:

\[ E[Y_t \mid A_1, A_2] = \beta_0 + \beta_1 S_1 + \beta_2 S_2 \]

- Slope at each stage should depend only on intervention options that have been assigned prior to that stage
Step #2: Select and fit a model

- Now, let’s consider incorporating the treatment assignment in:
  
  \[ E[Y_t | A_1, A_2] = \beta_0 + \beta_1 S_1 + \beta_2 S_2 \]

- Recall \( \beta_0 \) is the expected SP at beginning of school year
- \( \beta_0 \) should not vary depending on \( A_1 \) or \( A_2 \)
Step #2: Select and fit a model

- Now, let’s consider incorporating the treatment assignment in:

\[ E[Y_t \mid A_1, A_2] = \beta_0 + \beta_1 S_1 + \beta_2 S_2 \]

- Recall \( \beta_1 \) is the stage 1 slope
- \( \beta_1 \) can vary depending on \( A_1 \)
  - Replace \( \beta_1 \) by \((\beta_{10} + \beta_{11} A_1)\).

\[ = \beta_0 + (\beta_{10} + \beta_{11} A_1)S_1 + \beta_2 S_2 \]
Step #2: Select and fit a model

- Now, let’s consider incorporating the treatment assignment in:
  \[ E[Y_t \mid A_1, A_2] = \beta_0 + \beta_1 S_1 + \beta_2 S_2 \]

- Recall \( \beta_2 \) is the stage 2 slope
- \( \beta_2 \) can vary depending on \( A_1 \) and \( A_2 \)
  - Replace \( \beta_2 \) by \( (\beta_{20} + \beta_{21} A_1 + \beta_{22} A_2 + \beta_{23} A_1 A_2) \)
  
  \[ = \beta_0 + (\beta_{10} + \beta_{11} A_1) S_1 + (\beta_{20} + \beta_{21} A_1 + \beta_{22} A_2 + \beta_{23} A_1 A_2) S_2 \]
Step #3: Estimate linear combinations of parameters to compare AI #1 and AI #2

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Final example model:

$$E[Y_t|A_1, A_2] = \beta_0 + (\beta_{10} + \beta_{11}A_1)S_1 + (\beta_{20} + \beta_{21}A_1 + \beta_{22}A_2 + \beta_{23}A_1A_2)S_2$$
Longitudinal Outcome Analysis

**Step #3:** Estimate linear combinations of parameters to compare AI #1 and AI #2

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\]

Mean \( Y_3 \) under **AI #1 (MED, AUG)**

\[
= \beta_0 + (\beta_{10} + \beta_{11} \cdot -1) \cdot 2 + (\beta_{20} + \beta_{21} \cdot -1 + \beta_{22} \cdot -1 + \beta_{23} \cdot 1) \cdot 6
\]

\[
= \beta_0 + 2\beta_{10} - 2\beta_{11} + 6\beta_{20} - 6\beta_{21} - 6\beta_{22} + 6\beta_{23}
\]
Longitudinal Outcome Analysis

Step #3: Estimate linear combinations of parameters to compare AI #1 and AI #2

\[
E[Y_t|A_1, A_2] = \beta_0 + (\beta_{10} + \beta_{11}A_1)S_1 + (\beta_{20} + \beta_{21}A_1 + \beta_{22}A_2 + \beta_{23}A_1A_2)S_2
\]

Mean \( Y_3 \) under AI #2 (BMOD, AUG)

\[
= \beta_0 + (\beta_{10} + \beta_{11} \cdot 1) \cdot 2 + (\beta_{20} + \beta_{21} \cdot 1 + \beta_{22} \cdot -1 + \beta_{23} \cdot -1) \cdot 6
\]

\[
= \beta_0 + 2\beta_{10} + 2\beta_{11} + 6\beta_{20} + 6\beta_{21} - 6\beta_{22} - 6\beta_{23}
\]
Longitudinal Outcome Analysis

Step #3: Estimate linear combinations of parameters to compare AI #1 and AI #2

\[
E [Y_t|A_1, A_2] = \beta_0 + (\beta_{10} + \beta_{11} A_1)S_1 + (\beta_{20} + \beta_{21} A_1 + \beta_{22} A_2 + \beta_{23} A_1 A_2)S_2
\]

Difference in mean \(Y_3\) between AI#1 and AI#2

\[
= (\beta_0 + 2\beta_{10} - 2\beta_{11} + 6\beta_{20} - 6\beta_{21} - 6\beta_{22} + 6\beta_{23})
- (\beta_0 + 2\beta_{10} + 2\beta_{11} + 6\beta_{20} + 6\beta_{21} - 6\beta_{22} - 6\beta_{23})
= -4\beta_{11} - 12\beta_{21} + 12\beta_{23}
\]
Outline

• Brief review of using end-of-study outcome to compare embedded AIs

• Learn how to use repeated outcome measures from a SMART to compare embedded AIs

• **Review three types of scientific questions you can answer with repeated outcome measures**
  o Difference in end-of study outcome
  o Difference in Area Under the Curve (AUC)
  o Delayed effects

• Sample size considerations for planning SMARTs to compared embedded AIs with repeated outcome measures
Longitudinal Outcome Analysis

Area Under the Curve (AUC)

- Scientific Question: Is AI#1 better than AI#2 in terms of school performance averaged over the course of the intervention?
Longitudinal Outcome Analysis

Area Under the Curve (AUC)

- AI#1 AUC

***This example is hypothetical***
Longitudinal Outcome Analysis

Area Under the Curve (AUC)

- AI#1 AUC

***This example is hypothetical***
Longitudinal Outcome Analysis

**Area Under the Curve (AUC)**

- AI#2 AUC

***This example is hypothetical***
Longitudinal Outcome Analysis

**Area Under the Curve (AUC)**

- Difference in AUC AI#1-AI#2:

***This example is hypothetical***
Area Under the Curve (AUC)

- If you compare the two AIs in terms of end-of-school-year outcome, what would you conclude?
Longitudinal Outcome Analysis

Area Under the Curve (AUC)

- If you compare in terms of AUC...

***This example is hypothetical***
Longitudinal Outcome Analysis

**Area Under the Curve (AUC)**

- Consider when outcome values towards the middle (in the course of the school year) are considered more informative than are values that are at the end
Delayed Effects

- Scientific Question: Does the initial intervention options in AI #1 vs. AI #2 impact school performance differently before vs. after these AIs unfold?
  - before vs. after these AIs unfold → before vs. after second-stage options are introduced
Delayed Effects

- AI#1 & AI#2 lead to the same outcome at the end of school year
- But the process is different

***This example is hypothetical***
Delayed Effects

- Definition:
  - Difference between long-term effect and short-term effect
  - Difference between two differences

***This example is hypothetical***
Delayed Effects

• Difference between two differences

Long-term: Difference in mean $Y_3$ between AI#1 and AI#2

***This example is hypothetical***
Longitudinal Outcome Analysis

Delayed Effects

• Difference between two differences

Short-term: Difference in mean $Y_2$ between AI#1 and AI#2

***This example is hypothetical***
Longitudinal Outcome Analysis

**Delayed Effects**

- Difference between two differences

Long-term: Difference in mean $Y_3$ between **AI#1** and **AI#2**

- Short-term: Difference in mean $Y_2$ between **AI#1** and **AI#2**

***This example is hypothetical***
Delayed Effects

- Consider when there is scientific/practical rationale for positive or negative synergies between first and second stage options
Outline

• Brief review of using end-of-study outcome to compare embedded AIs

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• Sample size considerations for planning SMARTs to compared embedded AIs with repeated outcome measures
Longitudinal Outcome Sample Size for End-of-Study Comparisons

\[ N = \frac{4(z_{1-\alpha/2} + z_{1-\beta})^2}{\delta^2} \times (1 - \rho^2) \times (2 - r) \]

\( \delta \) is the standardized effect size for the comparison

\( \rho \) is the (compound-symmetric) within-person correlation

\( r \) is the probability of response to first-stage treatment
Longitudinal Outcome Sample Size for End-of-Study Comparisons

40% response rate
\( \alpha = 0.05 \) (two-sided)
80% target power

<table>
<thead>
<tr>
<th>Std. Effect Size</th>
<th>( \rho = 0 )</th>
<th>( \rho = 0.3 )</th>
<th>( \rho = 0.6 )</th>
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Longitudinal Outcome Sample Size for End-of-Study Comparisons

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\( \delta \) is the standardized effect size for the comparison

\( r \) is the probability of response to first-stage treatment
Additional Resources for Comparing Embedded AIs on a Longitudinal Outcome

R code for implementing the methodology
  • See John Dziak’s code here: http://d3lab-isr.com/resources/

Repeated measures variance estimation
  • Visit Nick Seewald’s poster

Random effects modeling
  • Visit Brook Luers’ poster

Visualizing data from a SMART to inform repeated measures mean and variance modeling
  • See Madison Stoms poster
Citations


