Advanced Topics In SMART Design and Data Analysis-- Part 1

How to use repeated outcome measures from a SMART to compare embedded AIs

Module 6
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
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
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
For simplicity assume response status was assessed at one time point (week 8).
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ADHD SMART
PI: Pelham

First-stage intervention

A1 = -1
MED

R = 1
Response

R = 0
Non-Response

A1 = 1
BMOD

R = 1
Response

R = 0
Non-Response

Intermediate outcome

R

Second-stage intervention

A2 = .
Continue

A2 = -1
Augment

A2 = 1
Intensify

A2 = .
Continue

A2 = -1
Augment

A2 = 1
Intensify

Experimental Conditions

Subgroups

A
B
C
D
E
F

Beginning of school year

O1

A1

O2 / R Status

A2

End of school year

Y
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: Assign weights 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 model parameters and linear combinations to compare AI #1 and AI #2

\[ E[Y|A_1, A_2] = \beta_0 + \beta_1 A_1 + \beta_2 A_2 + \beta_3 A_1 A_2 \]
End of Study Primary Outcome Analysis Review

**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) = \( \beta_0 + \beta_1(1) + \beta_2(-1) + \beta_3(1)(-1) \)
Step 3: Estimate linear combinations of parameters to compare AI #1 and AI #2

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

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
  - Difference in end-of-study outcome
  - Difference in Area Under the Curve (AUC)
  - Delayed effects
- Sample size considerations for planning SMARTs to compared embedded AIs with repeated outcome measures
Repeated Outcome Measures in a SMART = > before and after each randomization
Longitudinal Outcome Analysis

Step #1: Assign weights 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 weighted and replicated data would look like this:

<table>
<thead>
<tr>
<th>ID</th>
<th>Period</th>
<th>ODD at baseline</th>
<th>Response Status</th>
<th>School Perf</th>
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<tbody>
<tr>
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</tbody>
</table>
## Longitudinal Outcome Analysis

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

Fake weighted and replicated data would look like this:

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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
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

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

- 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.
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?*
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?
  - 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

- In the current example we have 2 intervals of primary interest:
Longitudinal Outcome Analysis

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

- In the current example we have 2 intervals of primary interest:

Interval 1: First-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

- In the current example we have 2 intervals of primary interest:

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

**Interval 2:** Second-stage intervention
Longitudinal Outcome Analysis

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

- In the current example we have 2 intervals of primary interest:

```
\begin{itemize}
  \item \textbf{Interval 1:} First-stage intervention
  \item \textbf{Interval 2:} Second-stage intervention
\end{itemize}
```

```
\begin{itemize}
  \item \textbf{Transition point}
  \item \textbf{Beginning of school year}
  \item \textbf{Week 8}
  \item \textbf{End of school year}
\end{itemize}
```

```
\begin{itemize}
  \item \textbf{Y1} \hspace{1cm} \textbf{A1} \hspace{1cm} \textbf{Y2 / R Status} \hspace{1cm} \textbf{A2} \hspace{1cm} \textbf{Y3}
\end{itemize}
```
Longitudinal Outcome Analysis

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

- In the current example we have 2 intervals of primary interest.
- The linear trend in the outcome during the first stage can vary from second-stage and be impacted by different variables.

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

- To fit a separate line for each interval: meet $S_1$ and $S_2$

**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

Hello!
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 $t$

<table>
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<tr>
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<th>2</th>
<th>8</th>
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</thead>
<tbody>
<tr>
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</tr>
<tr>
<td>$S_2$</td>
<td>0</td>
<td>0</td>
<td>6</td>
</tr>
</tbody>
</table>

**Interval 1:** First-stage intervention

Beginning of school year   Week 8   End of school year

**Interval 2:** Second-stage intervention

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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<td>0</td>
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<td>6</td>
</tr>
</tbody>
</table>

*Interval 1*: First-stage intervention

*Interval 2*: Second-stage intervention

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

$Y_1$  $A_1$  $Y_2$ / R Status  $A_2$  $Y_3$
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

The (fake) weighted and replicated data would look like this:

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</tbody>
</table>
Step #2: Select and fit a model

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

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

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

- Recall \( \beta_0 \) is the expected SP at beginning of school year
- \( \beta_0 \) should not vary depending on \( A_1 \) or \( A_2 \)
Longitudinal Outcome Analysis

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:

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

- 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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<tr>
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<tr>
<td>1</td>
<td>INTENSIFY</td>
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<tr>
<td>-1</td>
<td>AUGMENT</td>
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</table>

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

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

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

$$= \beta_0 + (\beta_{10} + \beta_{11} \times -1) \times 2 + (\beta_{20} + \beta_{21} \times -1 + \beta_{22} \times -1 + \beta_{23} \times 1) \times 6$$

$$= \beta_0 + 2\beta_{10} - 2\beta_{11} + 6\beta_{20} - 6\beta_{21} - 6\beta_{22} + 6\beta_{23}$$
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)**

$$= \beta_0 + (\beta_{10}+\beta_{11} * 1) * 2 + (\beta_{20}+\beta_{21} * 1 + \beta_{22} * -1 + \beta_{23} * -1) * 6$$

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

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

<table>
<thead>
<tr>
<th></th>
<th>$A_1$</th>
<th>$A_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BMOD</td>
<td>1</td>
</tr>
<tr>
<td>-1</td>
<td>MED</td>
<td>-1</td>
</tr>
</tbody>
</table>

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

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***
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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***
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Area Under the Curve (AUC)

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

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

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?
  o 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 $\text{AI#1}$ and $\text{AI#2}$

***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***
Delayed Effects

- Difference between two differences

Long-term: Difference in mean Y₃ between **AI#1** and **AI#2**

- Short-term: Difference in mean Y₂ between **AI#1** and **AI#2**

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

Delayed Effects

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

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  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 Sample Size for End-of-Study Comparisons

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

\(\delta\) 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>Within-Person Correlation</th>
<th></th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>( \delta = 0.3 )</td>
<td>( \rho = 0 )</td>
<td>559</td>
<td>508</td>
<td>358</td>
</tr>
<tr>
<td>( \delta = 0.5 )</td>
<td>( \rho = 0.3 )</td>
<td>201</td>
<td>183</td>
<td>129</td>
</tr>
</tbody>
</table>
Longitudinal Outcome Sample Size for End-of-Study Comparisons

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Citations


• Seewald, N. J., Kidwell, K.M., Nahum-Shani, I., Wu, T., McKay, J.R., Almirall, D. Sample Size Considerations for the Analysis of Continuous Repeated-Measures Outcomes in Sequential Multiple-Assignment Randomized Trials. *Statistical Methods in Medical Research*