40 minutes

This is the 5th module of a 5-module Seminar on experimental designs for building optimal adaptive health interventions. By now, you know what an ATS is. You have discussed why they are important in terms of managing chronic disorders (indeed, an ATS formalizes the type of clinical practice taking place today). And, you have been introduced to the SMART clinical trial design, the rationale for SMARTs, and some important SMART design principles.

By now you have also learned how to address 2 typical primary research questions (main effect of first line txt and effect of second-stage treatments (operationalized various ways, tactical and treatment))

By now you were also introduced to a weighting approach for estimating the mean outcome under 1 of the SMART design-embedded ATGs.

In this module, we are going to continue discussing the weighting approach. The goal is to continue to learn about this approach and learn how to use a weighting approach to estimate and compare the mean outcome for all of the design-embedded ATGs. This will be the final, 3rd, typical primary aim we discuss.
Primary Aims Part II, Outline

- Review the weighted regression approach for estimating the mean outcome had the entire population followed 1 of the embedded ATSs
- PII(a): Learn how to compare the mean outcome for two embedded ATSs that begin with different treatments using a weighting approach. (How to do this in one regression?)
- PII(b): Learn how to compare all of the SMART-embedded ATSs (simultaneously) using a weighting-and-replication approach
You were introduced to this SMART in modules 1, 2, 3, and 4.

Let’s review some of the characterizing features of this SMART design.
Recall Typical Primary Aim 3:
Best of two adaptive interventions?

• We seek to learn how to answer the question of which is the best of the following two “design-embedded” ATSs?

First treat with medication, then
  • If respond, then continue treating with medication
  • If non-response, then add behavioral intervention
versus

First treat with behavioral intervention, then
  • If response, then continue behavioral intervention
  • If non-response, then add medication

This primary aim is a comparison of 2 adaptive treatment strategies that begin with different first line treatment.

It is a comparison of two decision rules (notice the if/then).

One could also do all remaining pair-wise comparisons between the 4 embedded ATS. Here we chose 1 pair for illustration.
Already learned how to estimate the mean under red (MED,BMOD) ATS via weighting

- Assign \( W = \text{weight} = 2 \) to responders to MED
- Assign \( W = \text{weight} = 4 \) to non-responders to MED
- This “balances out” the responders and non-responders. Then we take \( W \)-weighted mean of sample who ended up in the 2 boxes.
Similar code can be used to estimate mean outcome under blue (BMOD, MED) ATS

[Diagram showing decision tree with options for medication, behavioral intervention, and outcomes such as responders and non-responders, with options to continue medication, increase medication dose, add behavioral intervention, continue behavioral intervention, increase behavioral intervention, and add medication.]
**Results: Estimate of mean outcome had population followed (BMOD, MED) ATS**

Analysis Of GEE Parameter Estimates

<table>
<thead>
<tr>
<th>Parameter Estimate</th>
<th>SError</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>0.0982</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Z1</td>
<td>0.4085</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Contrast Estimate Results

<table>
<thead>
<tr>
<th>95% Conf Limits</th>
<th>Estimate Lower</th>
<th>Upper</th>
<th>SError</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Y under the blue ATS</td>
<td>3.5067</td>
<td>3.1643</td>
<td>3.8490</td>
</tr>
</tbody>
</table>

This analysis is with simulated data.
You need to copy all of the SAS code from Pages 1 to 6 since we were just working with the Autism data set during the practicum and we want to avoid mixing up files. So this is like starting over. I will demonstrate...

Try it yourself in SAS

- Go to the file:
  “sas_code_modules_4_5_and_6_ADHD.doc”
- **Copy the SAS code from Page 1 through Page 6**
- Paste into SAS Enhanced Editor window
- Press F8 or click the Submit button (the little running man)
Results: Estimate of mean outcome had population followed (BMOD, MED) ATS

Analysis Of GEE Parameter Estimates

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<td>Intercept</td>
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<td>0.1070</td>
</tr>
<tr>
<td>Z1</td>
<td>0.4085</td>
<td>0.1070</td>
</tr>
</tbody>
</table>

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Primary Aims Part II, Outline

• Review the weighted regression approach for estimating the mean outcome had the entire population followed 1 of the embedded ATSS.

• PII(a): Learn how to compare the mean outcome for two embedded ATSSs that begin with different treatments using a weighting approach. (How to do this in one regression?)

• PII(b): Learn how to compare all of the SMART-embedded ATSSs (simultaneously) using a weighting-and-replication approach.
How do we compare mean outcomes for participants in red versus those in blue?
SAS code for a weighted regression to analyze Typical Primary Aim 3

```sas
data dat7; set dat2;
  Z1=-1; Z2=-1; W=4*R + 2*(1-R);
  if A1*R=-1 then Z1=1; if (1-A1)*(1-R)*A2=-2 then Z1=1;
  if A1*R= 1 then Z2=1; if (1+A1)*(1 R)*A2= 2 then Z2=1;
run;

data dat0; set dat7; if Z1=1 or Z2=1 run;
proc genmod data = dat8;
  class id;
  model y = z1;
  scwgt w;
  repeated subject = id / type = ind;
  estimate 'Mean Y under red ATS' intercept 1 z1 1;
  estimate 'Mean Y under blue ATS' intercept 1 z1 -1;
  estimate 'Diff: red - blue' z1 2;
run;
```

This analysis is with simulated data.

A key step: This regression should be done only with the participants following the red or the blue ATSs. Leave out others!
Following the blue ATS leads to better school performance than following the red. However, the difference is not statistically significant (p-value = 0.1756) at 5% Type-I error.

It is also possible to adjust for baseline (pre-A1) covariates in this regression. This usually leads to more efficient (more statistically powerful) comparisons, if the covariate is predictive of the outcome.
Try it yourself in SAS

- Go to the file:
  “sas_code_modules_4_5_and_6_ADHD.doc”
- **Copy the SAS code on Page 7**
- Paste into SAS Enhanced Editor window
- Press F8 or click the Submit button (the little running man)
Note the mean under the red ATS is identical to what we found in the previous module.

Following the blue ATS leads to better school performance than following the red. However, the difference is not statistically significant (p-value = 0.1756) at 5% Type-I error.

It is also possible to adjust for baseline (pre-A1) covariates in this regression. This usually leads to more efficient (more statistically powerful) comparisons, if the covariate is predictive of the outcome.
Primary Aims Part II, Outline

• Review the weighted regression approach for estimating the mean outcome had the entire population followed 1 of the embedded ATSSs

• PII(a): Learn how to compare the mean outcome for two embedded ATSSs that begin with different treatments using a weighting approach. (How to do this in one regression?)

• PII(b): Learn how to compare all of the SMART-embedded ATSSs (simultaneously) using a weighting-and-replication approach
What about a regression that allows comparison of mean under all four ATSs?
What about a regression that allows comparison of mean under all four ATSs?
Note that all responders are consistent with 2 of the embedded ATS. For example, ...

- Medication
  - Responders
    - Continue Medication
    - Increase Medication Dose (Add Behavioral Intervention)
  - Non-Responders
    - R

- Medication
  - Responders
    - Continue Medication
    - Increase Medication Dose
  - Non-Responders
    - R
    - Add Behavioral Intervention
So, since all responders are consistent with 2 of the embedded ATSs, we...

- We just need to “trick” or “explain” this to SAS
- Do this by replicating responders:
  - Create 2 observations for each responder
  - We assign ½ of them A2=1, the other ½ A2=-1
  - As before, assign W=2 to responders and W=4 to non-responders
- Robust standard errors take care of the fact that we are “re-using” the responders. No cheating here!
Pictorially, what does the replication do?

Medication

Responders → Continue MED

Non-Responders → Increase MED

Add BMOD

Medication

Responders → Continue MED

Non-Responders → Increase MED

Add BMOD
Basically we require an extra step to replicate observations (i.e., rows in the data set) of responders, such that instead of one observation per responder, there are 2 observations per responder (one with A2=1 and the other with A2=-1).

The working intuition is that since a responder’s treatment is consistent with this person having been assigned either of two ATSs, then we need use each responder’s data twice. The first time to estimate the mean for the first ATS and the second time to estimate the mean for the second ATS.
Try it yourself in SAS

- Go to the file: “sas_code_modules_4_5_and_6_ADHD.doc”
- **Copy the SAS code on Page 8**
- Paste into SAS Enhanced Editor window
- Press F8 or click the Submit button (the little running man)

In the SAS output window, you can see how certain participants were replicated and others were not. Let’s look at that together before moving on to the next slide.
After replication-and-weighting, the SAS code for the weighted regression to estimate mean under all four ATs is easy!

```sas
proc genmod data = dat9;
  class id;
  model y = a1 a2 a1*a2;
  scwgt weight;
  repeated subject = id / type = ind;
  estiuncate 'Mean Y under red' ATS' int 1 a1 1 a2 1 a1*a2 1;
  estimate 'Mean Y under blue' ATS' int 1 a1 1 a2 -1 a1*a2 -1;
  estimate 'Mean Y under green' ATS' int 1 a1 -1 a2 1 a1*a2 -1;
  estimate 'Mean Y under orange' ATS' int 1 a1 1 a2 1 a1*a2 1;
  estimate 'Diff: red - blue' int 0 a1 -2 a2 0 a1*a2 0;
  estimate 'Diff: orange - blue' int 0 a1 0 a2 2 a1*a2 2;
  estimate 'Diff: green - blue' int 0 a1 -2 a2 2 a1*a2 0;
  * etc...;
run;
```

* This analysis is with simulated data.

* Why only four parameters? Because there are only 4 means in total that we wish to estimate.
**Results:** replication-and-weighting to estimate mean outcome under all 4 ATs

<table>
<thead>
<tr>
<th>Contrast Estimate Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>95% Conf Limits</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Mean Y under red</td>
</tr>
<tr>
<td>Mean Y under blue</td>
</tr>
<tr>
<td>Mean Y under green</td>
</tr>
<tr>
<td>Mean Y under orange</td>
</tr>
<tr>
<td>Diff: red - blue</td>
</tr>
</tbody>
</table>

**NOTE:** We get the exact same results as before when we compared red vs blue, but now we can simultaneously make inference for all the comparisons.

This analysis is with simulated data.
Try it yourself in SAS

• Go to the file:
  “sas_code_modules_4_5_and_6_ADHD.doc”
• **Copy the SAS code on Page 9**
• Paste into SAS Enhanced Editor window
• Press F8 or click the Submit button (the little running man)
Results: replication-and-weighting to estimate mean outcome under all 4 ATSs

<table>
<thead>
<tr>
<th></th>
<th>Estimate</th>
<th>Lower</th>
<th>Upper</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Y under red</td>
<td>2.8649</td>
<td>2.5305</td>
<td>3.1992</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean Y under blue</td>
<td>3.5007</td>
<td>3.1643</td>
<td>3.8490</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean Y under green</td>
<td>2.7895</td>
<td>2.4644</td>
<td>3.1145</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean Y under orange</td>
<td>2.6533</td>
<td>2.2515</td>
<td>3.0552</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Diff: red - blue</strong></td>
<td>-0.6418</td>
<td>-1.1203</td>
<td>-0.1633</td>
<td>0.0086</td>
</tr>
</tbody>
</table>

**NOTE:** We get the exact same results as before when we compared red vs blue, but now we can simultaneously make inference for all the comparisons.

This analysis is with simulated data.
Replication-and-weighting to estimate outcome under all 4 ATSe with more power

```plaintext
proc genmod data = dat7;
  class id;
  model y = a1 a2 a1*a2 012c 014c;
  scwgt weight;
  repeated subject = id / type = ind;
  estimates 'Mean Y under red ATS' int 1 a1 1 a2 1 a1*a2 1;
  estimates 'Mean Y under blue ATS' int 1 a1 1 a2 -1 a1*a2 -1;
  estimates 'Mean Y under green ATS' int 1 a1 -1 a2 1 a1*a2 -1;
  estimates 'Mean Y under orange ATS' int 1 a1 1 a2 1 a1*a2 1;
  est开始' Diff: red - blue' a2 2 a2 2 a1*a2 2;
  estimates 'Diff: orange - blue' int 0 a1 0 a2 2 a1*a2 2;
  estimates 'Diff: green - blue' int 0 a1 -2 a2 2 a1*a2 0;
* etc...;
run;
```

This analysis is with simulated data.

Improve efficiency: Adjusting for baseline covariates that are associated with outcome leads to more efficient estimates (lower standard error = more power = smaller p-value).
Results: more powerful wtd. Regression to estimate mean outcome under all 4 ATs

**Improved efficiency:**
Adjusting for baseline covariates resulted in tighter confidence intervals. Point estimates remained about the same, as expected.

<table>
<thead>
<tr>
<th>Mean Y under red ATS</th>
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<th>Upper</th>
<th>P-value</th>
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<tbody>
<tr>
<td></td>
<td>2.8801</td>
<td>2.5869</td>
<td>3.1733</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean Y under blue ATS</td>
<td>3.3864</td>
<td>3.0689</td>
<td>3.7018</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean Y under green ATS</td>
<td>2.8140</td>
<td>2.5163</td>
<td>3.1135</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean Y under orange ATS</td>
<td>2.7338</td>
<td>2.3596</td>
<td>3.1081</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diff: red - blue</td>
<td>-0.5053</td>
<td>-0.9401</td>
<td>-0.0701</td>
<td>0.0228</td>
</tr>
</tbody>
</table>

etc...

etc...

This analysis is with simulated data.
Try it yourself in SAS

• Go to the file:
  sas_code_modules_4_5_and_6_ADHD.doc
• **Copy the SAS code on Page 10**
• Paste into SAS Enhanced Editor window
• Press F8 or click the Submit button (the little running guy)
Results: **more powerful** wtd. Regression to estimate mean outcome under all 4 ATSSs

*Improved efficiency:* Adjusting for baseline covariates resulted in tighter confidence intervals. Point estimates remained about the same, as expected.

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*This analysis is with simulated data.*
Citations


  – Technical Report available at the Methodology Center, PSU
Practicum

*Autism Exercises:* As before, we will go through the Autism Starter File to continue practicing/working through these primary data analyses using the Autism data set.