Secondary Aims Using Data Arising from a SMART

Module 5

General Objectives

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

Outline

Discuss moderators analysis in the context of a SMART

Discuss the idea of “a more deeply-tailored AI”

Q-Learning

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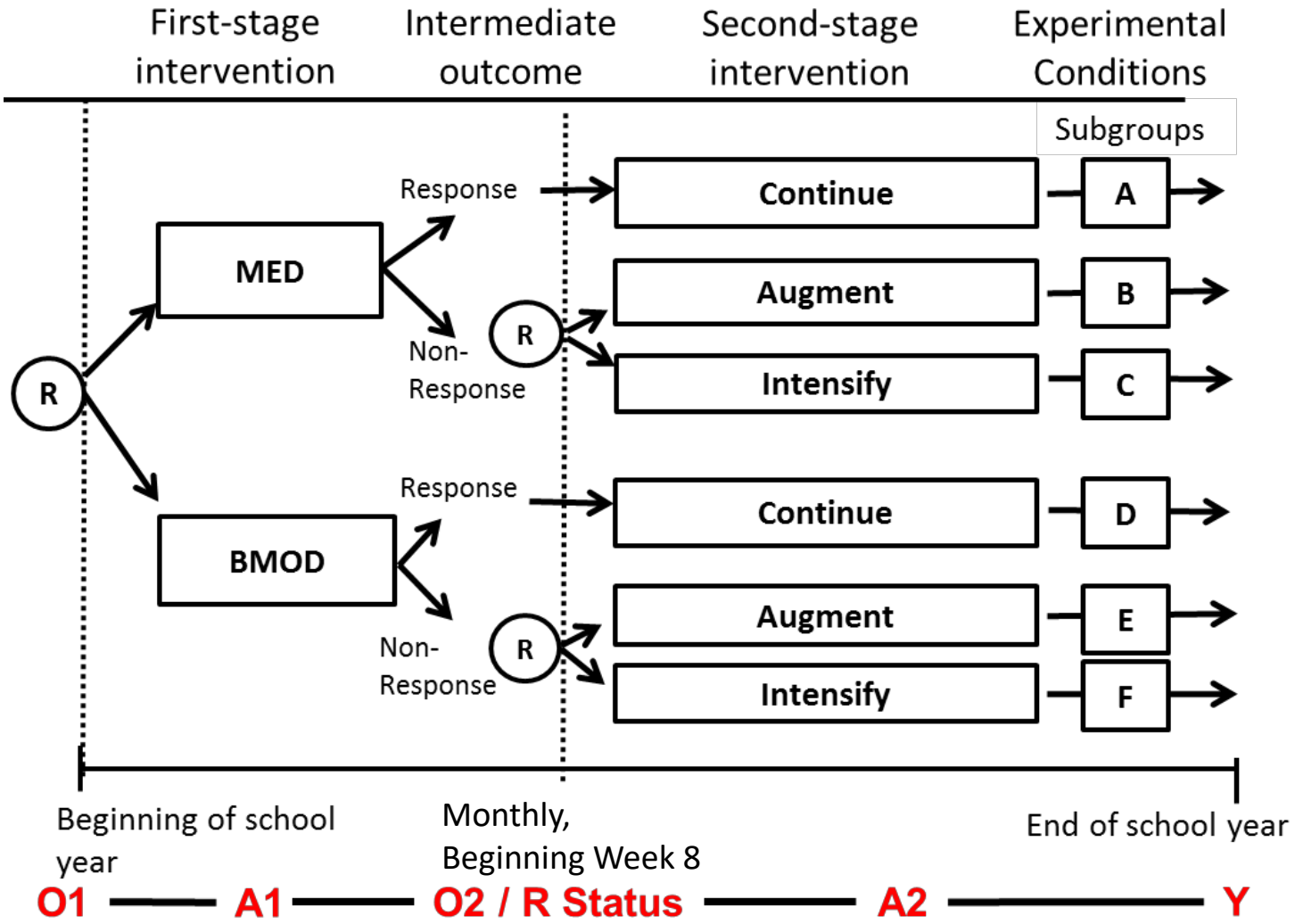
Discuss moderators analysis in the context of a SMART

Discuss the idea of “a more deeply-tailored AI”

Q-Learning

Remember ADHD SMART?



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

ADHD SMART

PI: Pelham

4 embedded adaptive interventions

AI #1:

Start with MED;

if non-responder AUGMENT, else CONTINUE

AI #2:

Start with BMOD;

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AI #3:

Start with MED;

if non-responder INTENSIFY, else CONTINUE

AI #4:

Start with BMOD;

if non-responder INTENSIFY, else CONTINUE

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Moderator analyses dive deeper…

1. It may be that some participants may benefit more from starting on MED vs. starting on BMOD.

   For example: those who have used MED in the past

2. Certain types of non-responders may also benefit more from AUGMENT vs. INTENSIFY

   For example: those who do not adhere to initial treatment

These analyses may suggest new tailoring variables that we should use in our AI.

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Discuss moderators analysis in the context of a SMART

Discuss the idea of “a more deeply-tailored AI”

Q-Learning

What is a more deeply-tailored AI?

In the ADHD SMART, there is only 1 tailoring variable embedded *by design* in the embedded AIs

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

What is a more deeply-tailored AI?

A more **deeply tailored AI** is a sequence of decision rules that include tailoring variables **beyond those** embedded in the SMART *by design*.

- i.e., an AI that tailors treatment to **Response Status AND** *additional variables*

For example, I want to investigate whether to tailor based on:

- First stage MED vs. BMOD on prior receipt of medication; and
- Second stage INT vs. AUG on first-stage adherence.

The embedded AI looked like this:

At the beginning of school year,

Stage 1 = {BMOD}.

Then, every month,
beginning at week 8

IF response status to Stage 1 = {NR}

THEN Stage 2 = {AUGMENT}.

ELSE CONTINUE Stage 1.

A (hypothetical) more deeply-tailored AI might look like this:

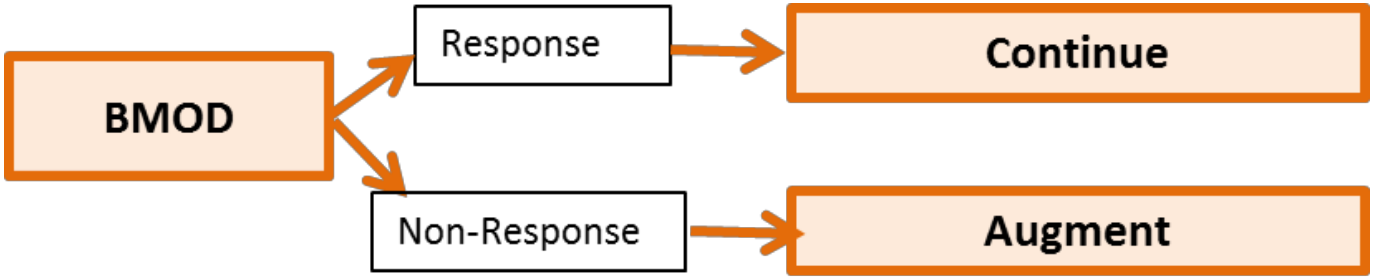
At the beginning of school year

IF **medication in prior year** = {NO}
THEN stage 1 = {BMOD}.
ELSE IF **medication in prior year** ={YES}
THEN stage 1 = {MED}

Then, every month,
beginning at week 8

IF **response status** to Stage 1 = {NR}
THEN IF **adherence** to stage 1 = {NO},
THEN Stage 2 = {AUGMENT}.
ELSE Stage 2 = {AUGMENT} or {INTENSIFY}.
ELSE CONTINUE Stage 1.

An Embedded AI:



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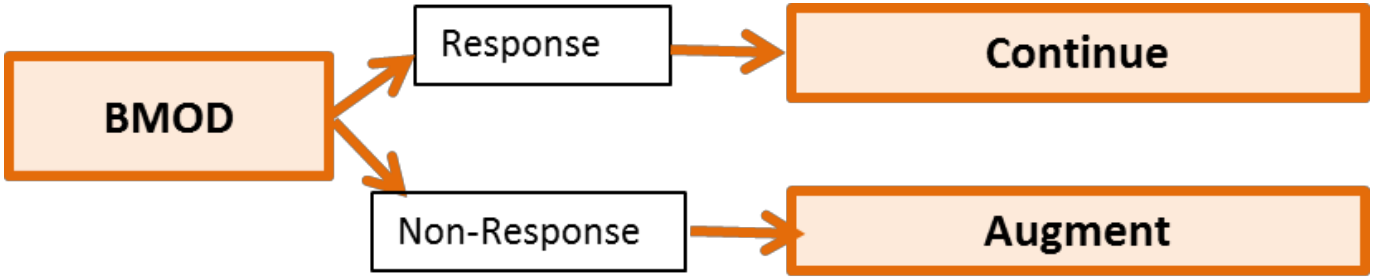
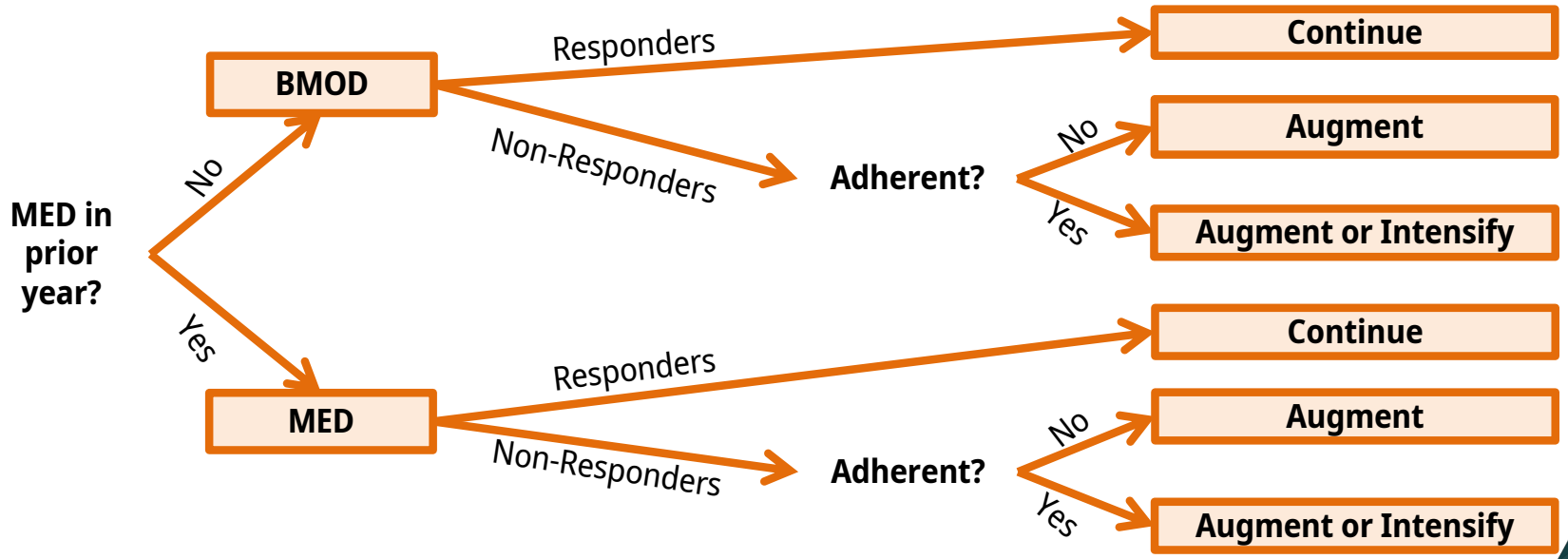


A More Deeply-Tailored AI:



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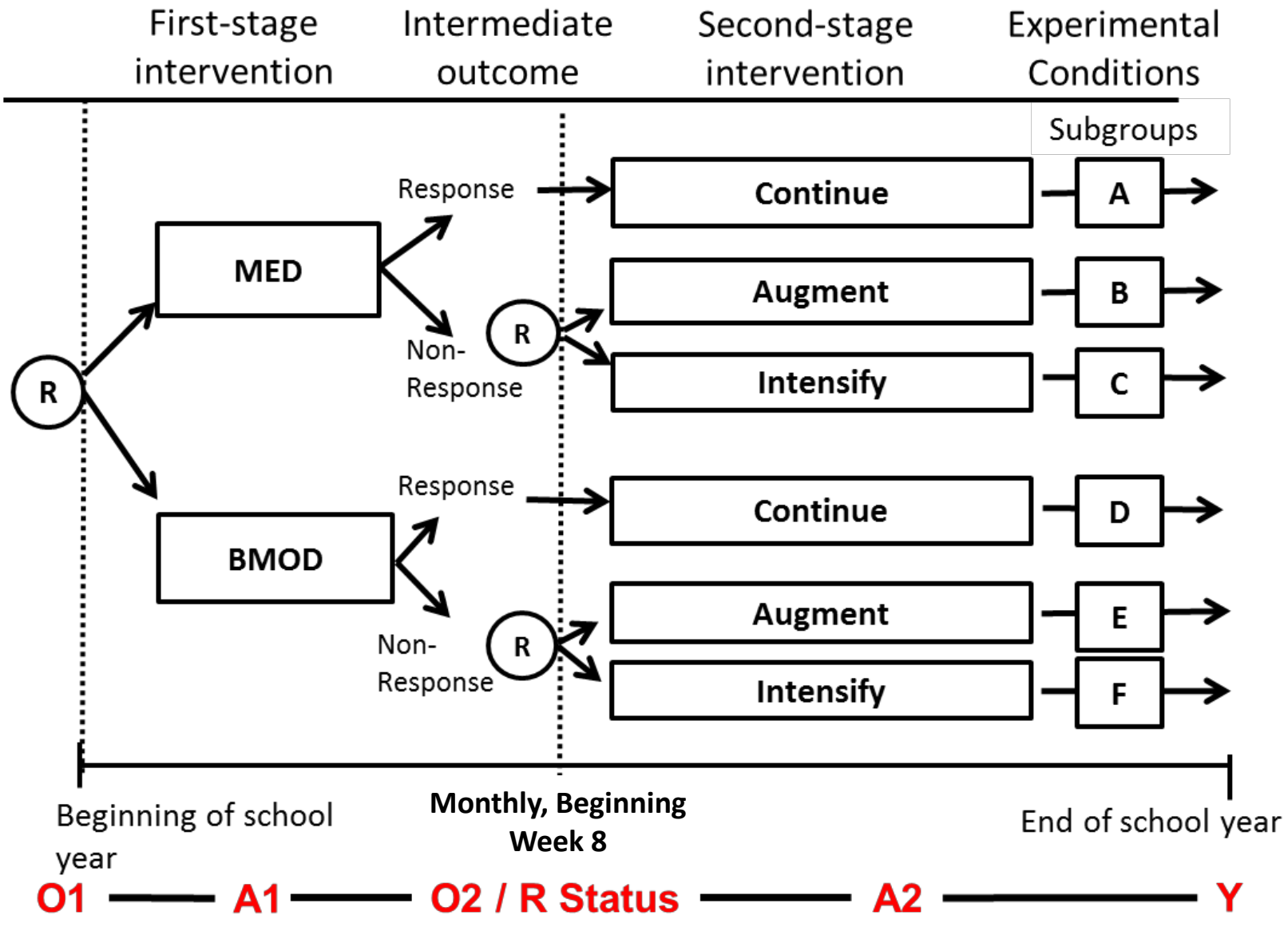
Q-Learning

Other measures collected in a SMART



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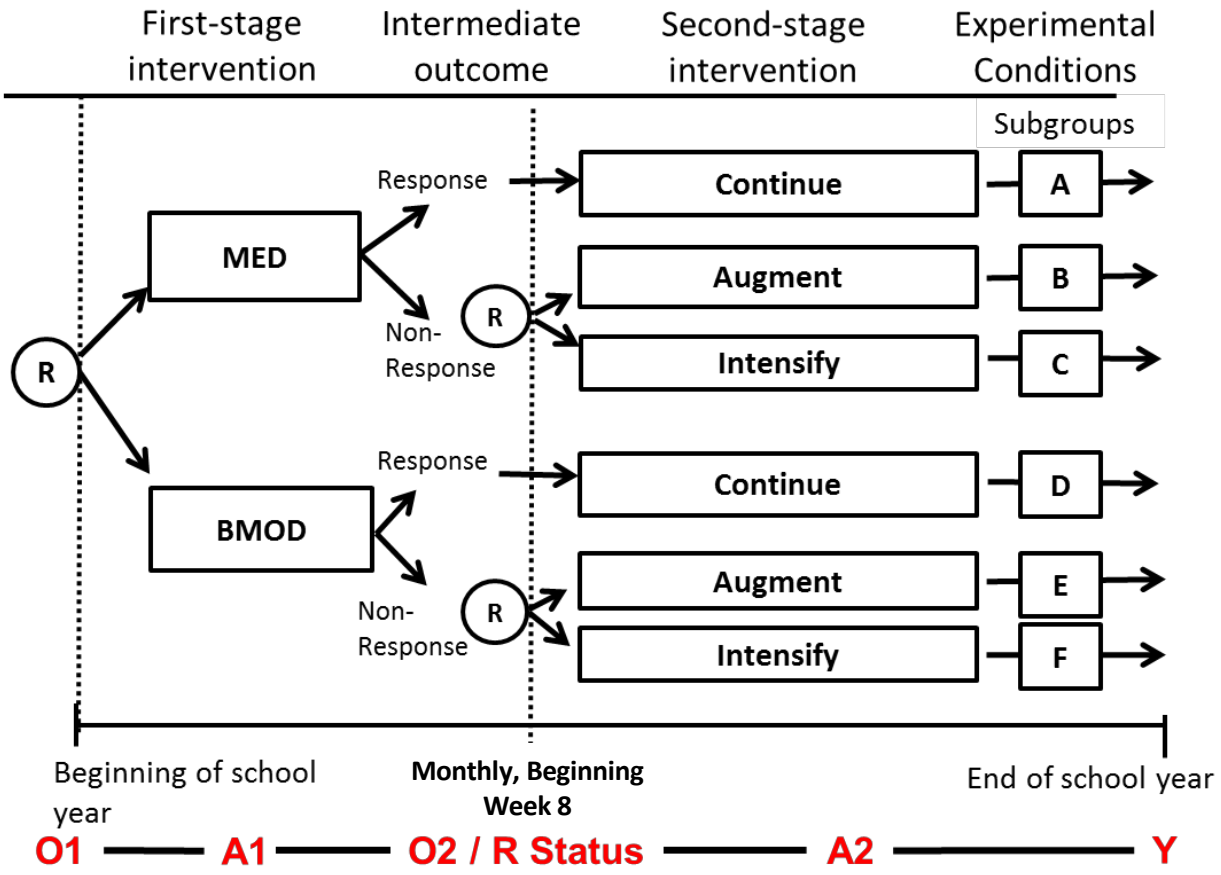
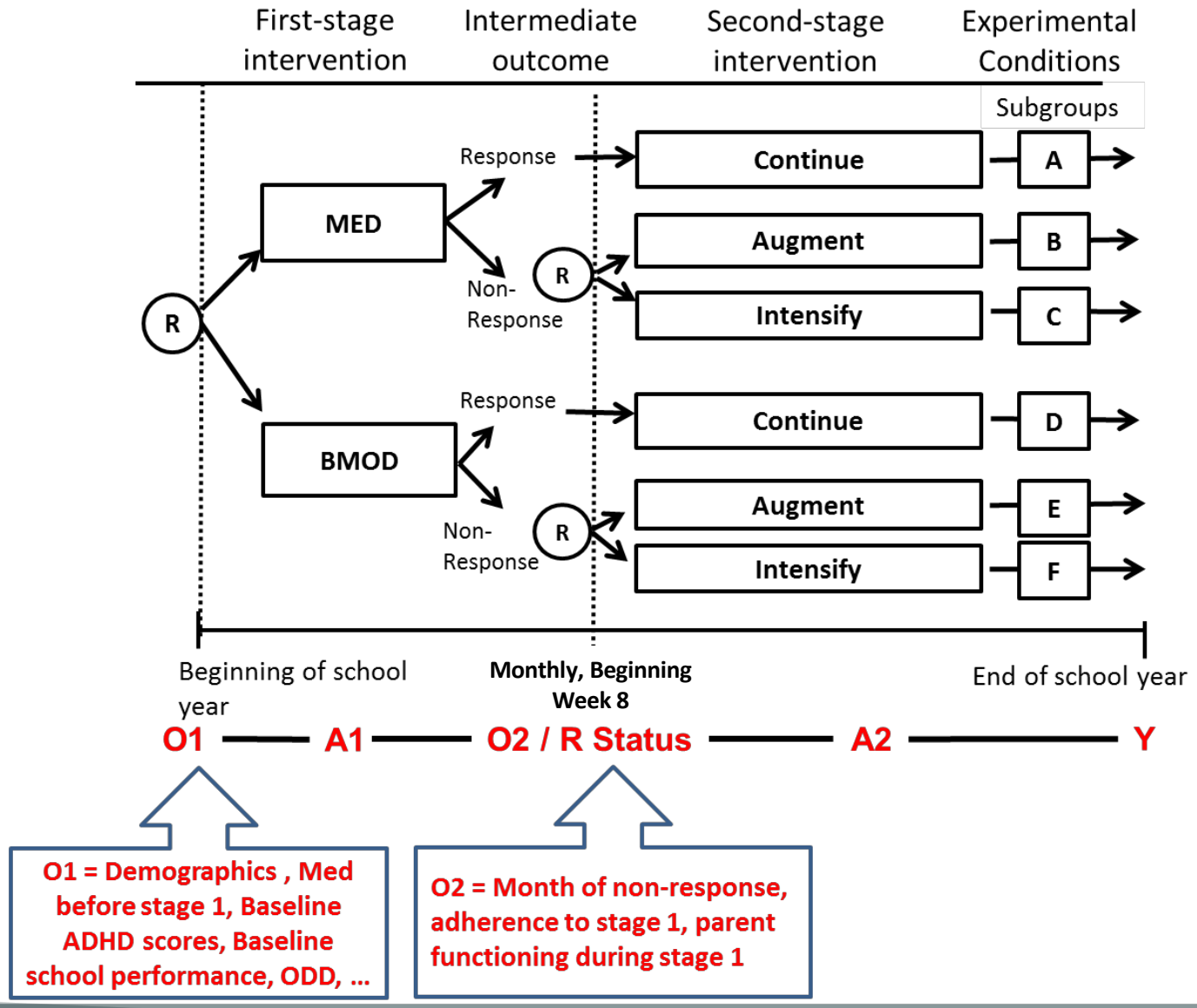


O1 = Demographics , Med before stage 1, Baseline ADHD scores, Baseline school performance, ODD, …

Other measures collected in a SMART



How should we use O1 and O2?

Auxiliary data from **O1** can help decide **who would *benefit more* from MED vs. BMOD**

- *Our example:* Medication in the prior year

Auxiliary data from **O1 and O2** can help decide **which *non-responders* would *benefit more* from INTENSIFY vs. AUGMENT**

- *In addition* to using information on first-stage treatment assignment
- *Our example*: Adherence to Stage One treatment

How do we do baseline moderators analysis?

If the goal is to examine only baseline moderators, $\boldsymbol{O_1}$, one could use a single regression:

$$E[\,Y \mid \boldsymbol{O_1}, A_1, A_2\,] = \beta_0 + \beta_1 \boldsymbol{O_1} + \beta_2 A_1 + \beta_3 \boldsymbol{O_1} \boldsymbol{A_1} + \beta_4 A_2 + \beta_5 A_1 A_2$$

This would allow us to examine baseline **O1** variables as moderators of **first-stage treatment**.

Baseline and time-varying moderators analysis?

If the goal is to examine baseline and time-varying moderators, the instinct might be to do this in a single regression as follows:

$$E[\,Y \mid \boldsymbol{O_1}, A_1, \boldsymbol{O_2}, A_2\,] = \beta_0 + \beta_1 \boldsymbol{O_1} + \beta_2 A_1 + \beta_3 \boldsymbol{O_1} A_1 + \beta_4 \boldsymbol{O_2} + \beta_5 A_2 + \beta_6 \boldsymbol{O_2} A_2 + \beta_7 A_1 A_2$$

The hope is that this would allow us to examine baseline **O1** variables as moderators of **first-stage treatment** & time-varying **O2** variables as moderators of **second-stage treatment**.

What's the problem with this approach?

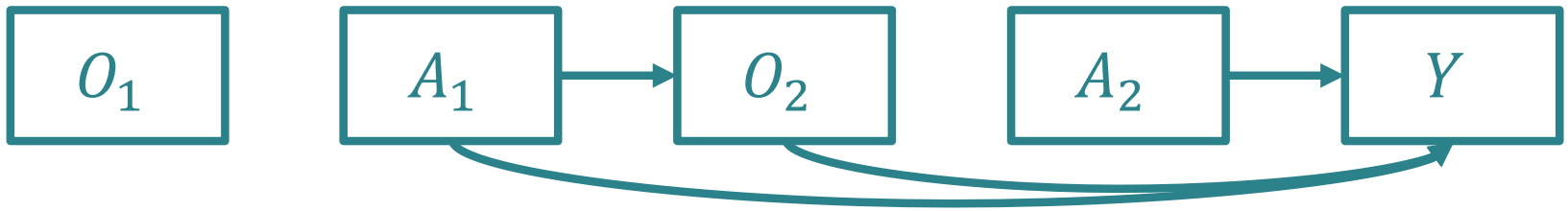
Baseline and time-varying moderators analysis?

Instinct might be to do this in a single regression:

$$E[\,Y \mid \boldsymbol{O_1}, A_1, \boldsymbol{O_2}, A_2\,] = \beta_0 + \beta_1 \boldsymbol{O_1} + \beta_2 A_1 + \beta_3 \boldsymbol{O_1 A_1} + \beta_4 \boldsymbol{O_2} + \beta_5 A_2 + \beta_6 \boldsymbol{O_2 A_2} + \beta_7 A_1 A_2$$

O2 happens *after* **A1**

- Potential mediator of relationship between A1 and Y



Baseline and time-varying moderators analysis?

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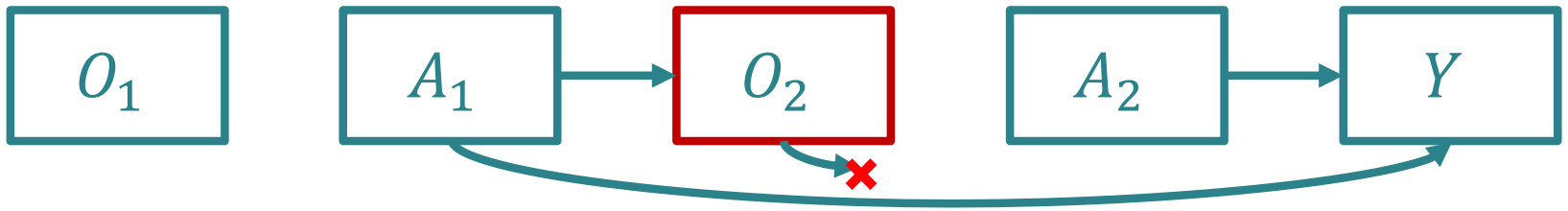
O2 happens *after* **A1**

- Potential mediator of relationship between A1 and Y
- Thus, (β_2, β_3) do not have the causal interpretation one wants
    - Because conditioning naively on O2 "cuts-off" the indirect effect of A1 on Y via O2



Baseline and time-varying moderators analysis?

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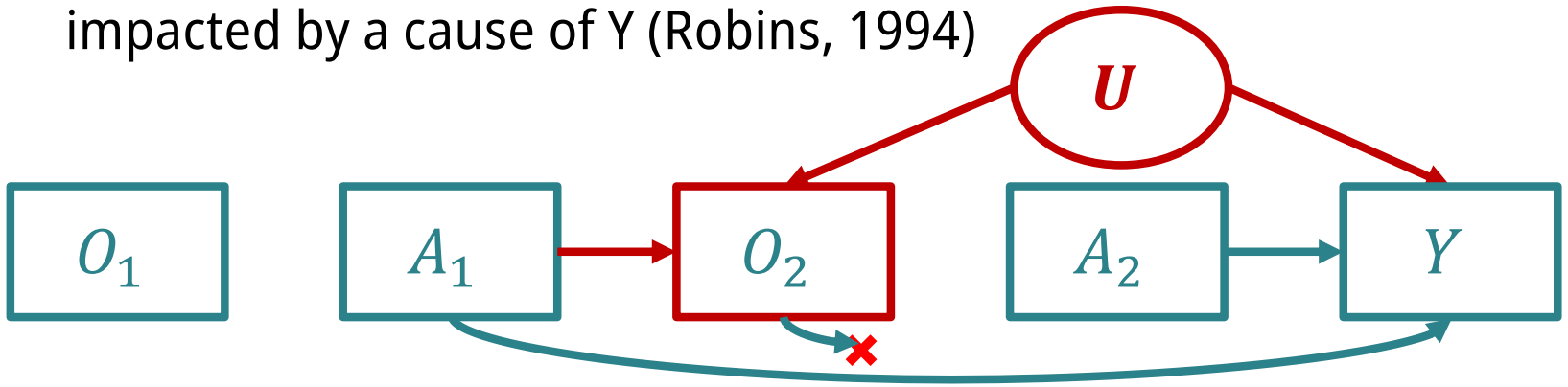
O2 happens *after* **A1**

- Collider Bias: A spurious (non-causal) correlation between A1 and Y resulting from conditioning naively on an outcome of A1 that is also impacted by a cause of Y (Robins, 1994)



Baseline and time-varying moderators analysis?

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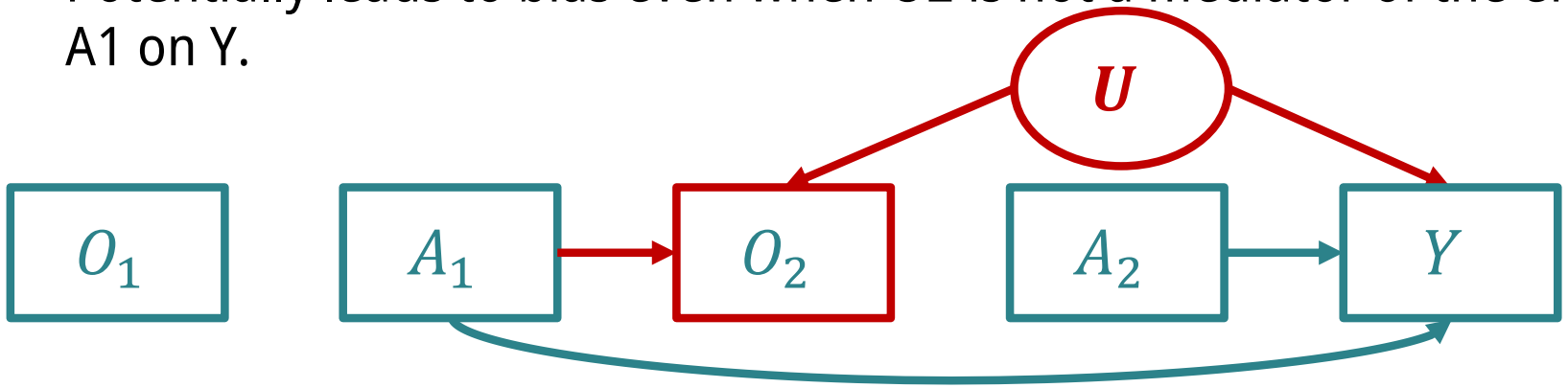
O2 happens *after* **A1**

- Collider Bias (Robins, 1994)
- Potentially leads to bias even when O2 is not a mediator of the effect of A1 on Y.



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What is Q-Learning?

- Extends regression to **sequential treatments**
- “Q” = “Quality”
- Hypothesis-generating

What is Q-Learning?

The results of Q-Learning ***propose an AI*** with greater treatment individualization

- i.e., an AI that includes more tailoring variables than the AIs embedded in the SMART *by design*

Q-Learning has 3 steps

Step 1

- ***Second-Stage Regression***
  - Are **O1, A1, and O2** useful in making decisions about second-stage tactics?
  - (Are **O1, A1, and O2** useful in deciding **which NR** would benefit from Augment vs. Intensify?)

Step 2

- ***Calculate*** $\hat{Y}_i$
  - What would the outcome be if they had received the best second-stage tactic given **O1, A1, and O2?**
  - **$\hat{Y}_i$ is the estimated optimal outcome under the best second-stage tactic for non-responders.** ($\hat{Y}_i$=Y for responders)

Step 3

- ***First-Stage Regression***
  - Is **O1** useful in making decisions about first-stage tactics, *assuming we use optimal second-stage tactic*? (Use **$\hat{Y}_i$** from Step 2 as the outcome!)
  - (Is **O1** useful in deciding who would benefit from MED vs. BMOD, *assuming NRs get the best second-stage treatment*?)

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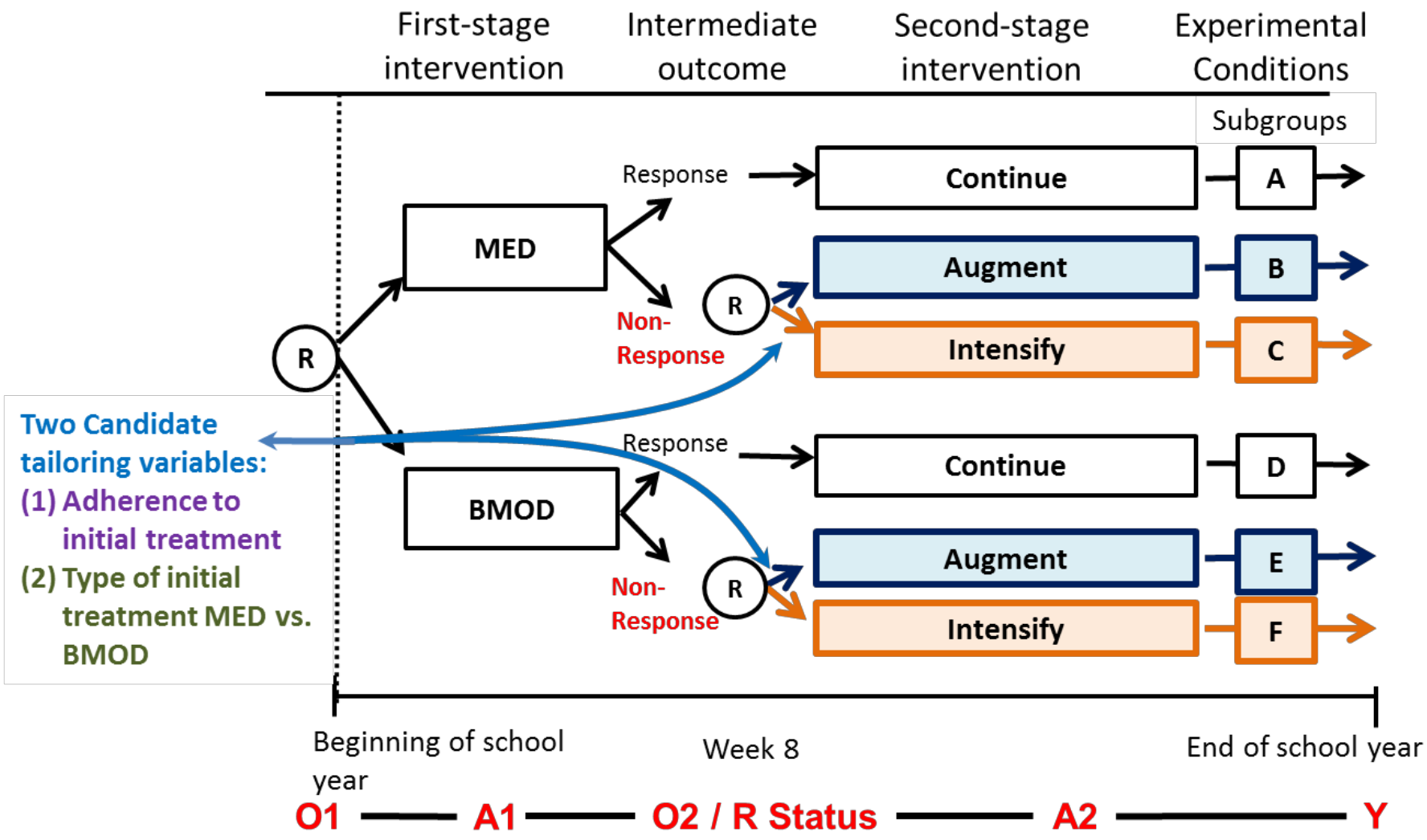
Step 1: Second-stage tailoring



Step 1: Second-stage tailoring

In this step, we want to address 2 questions:

1. Can we use information about **adherence** to initial treatment to *select a tactic for non-responders*?
2. Can we use information about the **initial treatment** to *select a tactic for non-responders*?

Step 1: Second-stage tailoring

In this step, we want to address 2 questions:

1. Can we use information about **adherence** to initial treatment to *select a tactic for non-responders*?
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To do this: Fit a **moderators analysis** using data from non-responders

See next slide for details…

Step 1: Second-stage tailoring

In this step, we want to address 2 questions:

1. Can we use information about **adherence** to initial treatment to *select a tactic for non-responders*?
2. Can we use information about the **initial treatment** to *select a tactic for non-responders*?

To do this: Fit a **moderated regression model** using data from non-responders

$$E[\,Y \mid O_1, A_1, O_2, A_2\,]$$
$$= \beta_0 + \beta_1 O_{11c} + \beta_2 O_{12c} + \beta_3 O_{13c} + \beta_4 O_{14c} + \beta_5 O_{12c}$$
$$+\beta_6 O_{21c} + \beta_7 \boldsymbol{A_1} + \beta_8 \boldsymbol{O_{22}}$$
$$+\beta_9 A_2 + \beta_{10}(A_2 \times \boldsymbol{A_1}) + \beta_{11}(A_2 \times \boldsymbol{O_{22}})$$

Step 1: Second-stage tailoring

$$E[\,Y \mid O_1, A_1, O_2, A_2\,] = \beta_0 + \cdots + \beta_7 \boldsymbol{A_1} + \beta_8 \text{adherence} + \beta_9 A_2 + \beta_{10}(A_2 \times \boldsymbol{A_1}) + \beta_{11}(A_2 \times \text{adherence})$$

A1 = Stage 1 options: -1=MED; 1=BMOD

A2 = Stage 2 options: -1=ADD; 1=INTSFY

Adherence to Stage 1: 1=yes; 0=no

Y = End of year school performance

Step 1: Second-stage tailoring

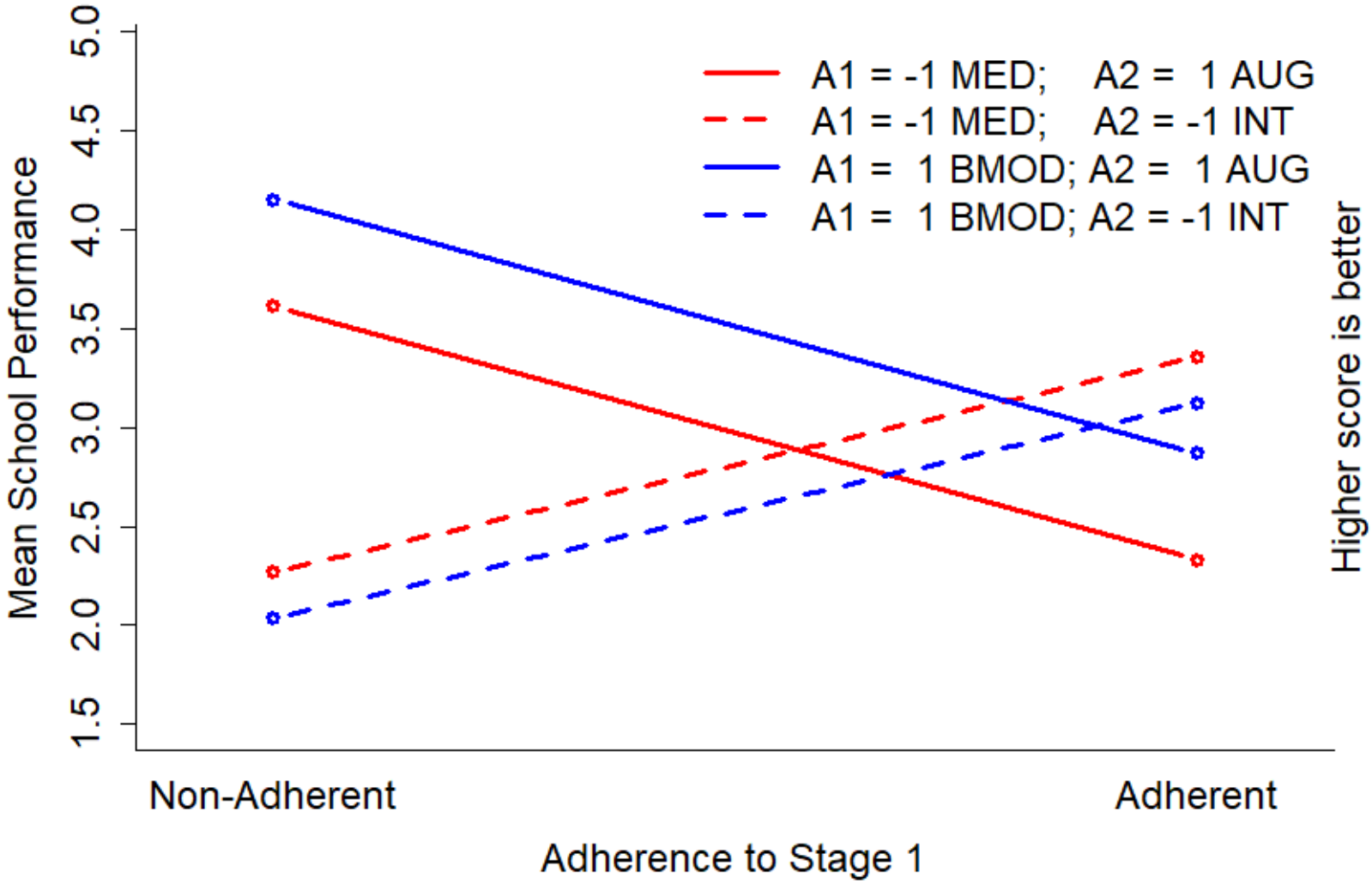
$$E[\,Y \mid O_1, A_1, O_2, A_2\,] = \beta_0 + \cdots + \beta_7 A_1 + \beta_8 \text{adherence} + \beta_9 A_2 + \beta_{10}(A_2 \times A_1) + \beta_{11}(A_2 \times \text{adherence})$$

A1 = Stage 1 options: -1=MED; 1=BMOD
A2 = Stage 2 options: -1=ADD; 1=INTSFY
Adherence to Stage 1: 1=yes; 0=no
Y = End of year school performance

This model will help us to:

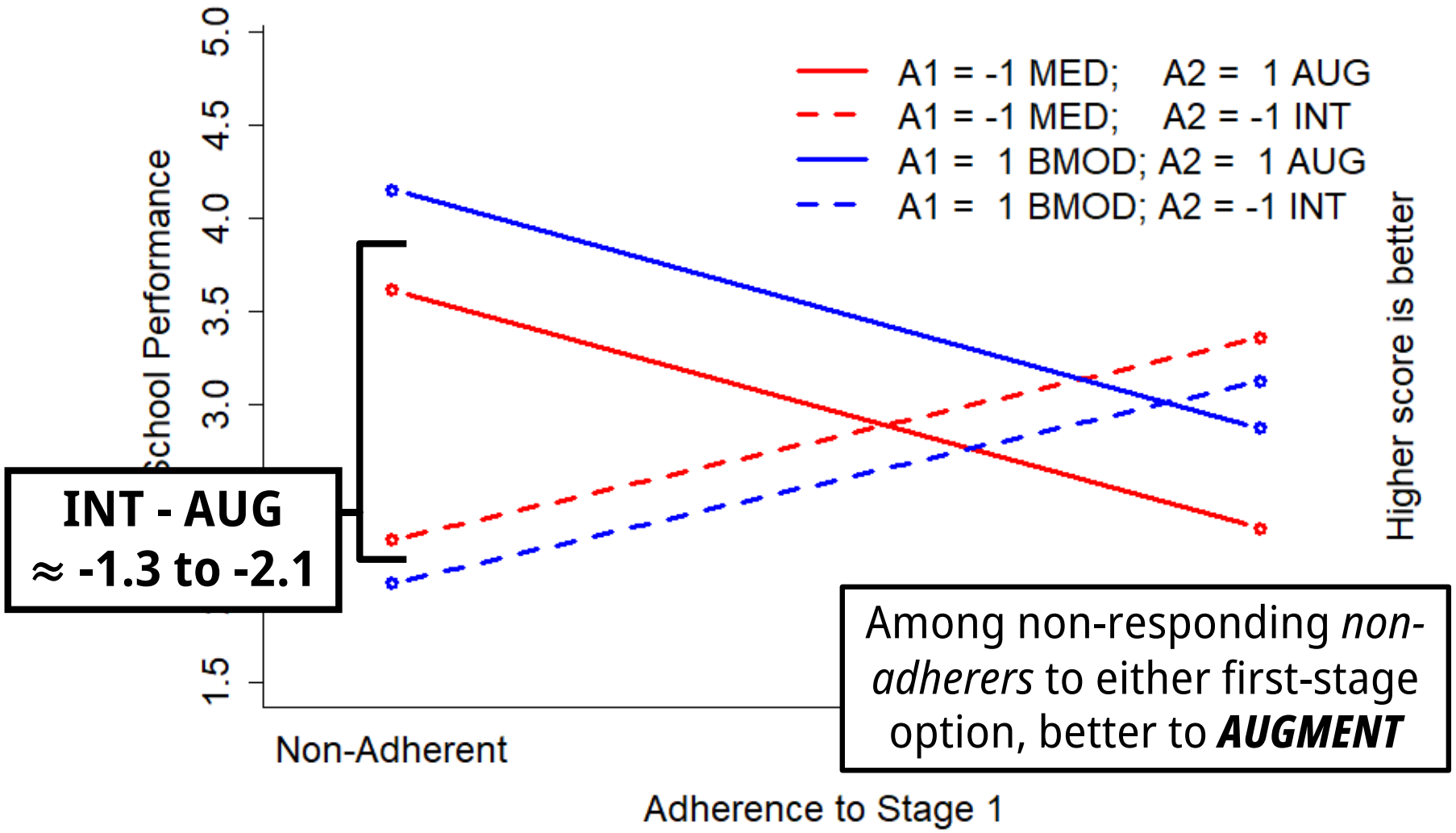
a) Determine whether the best second stage tactics varies depending on the tailoring variables; and
b) Identify the best second-stage tactic for each level of the tailoring variable

Step 1: Second-stage tailoring



This analysis is with simulated data.

Step 1: Second-stage tailoring



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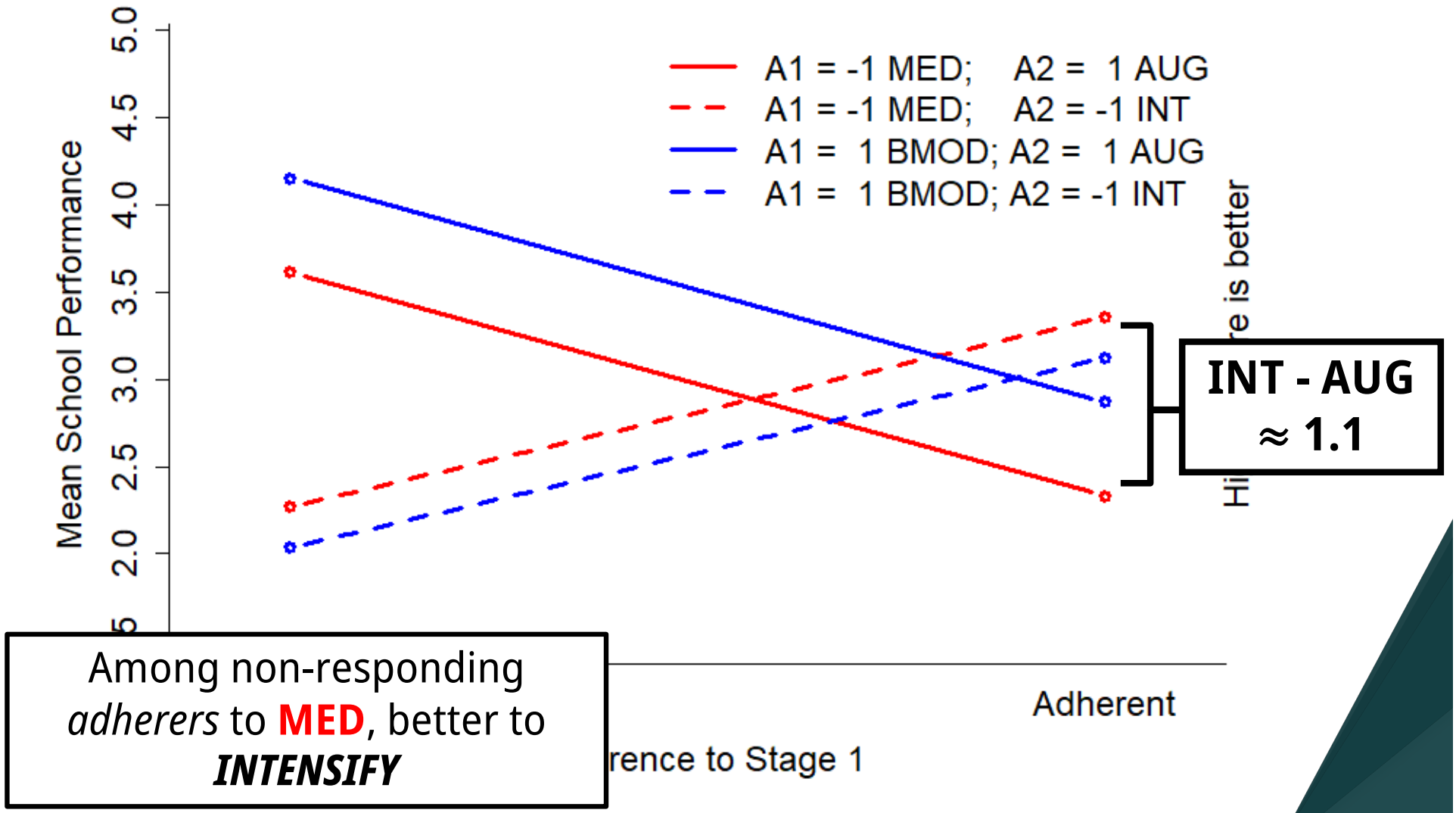
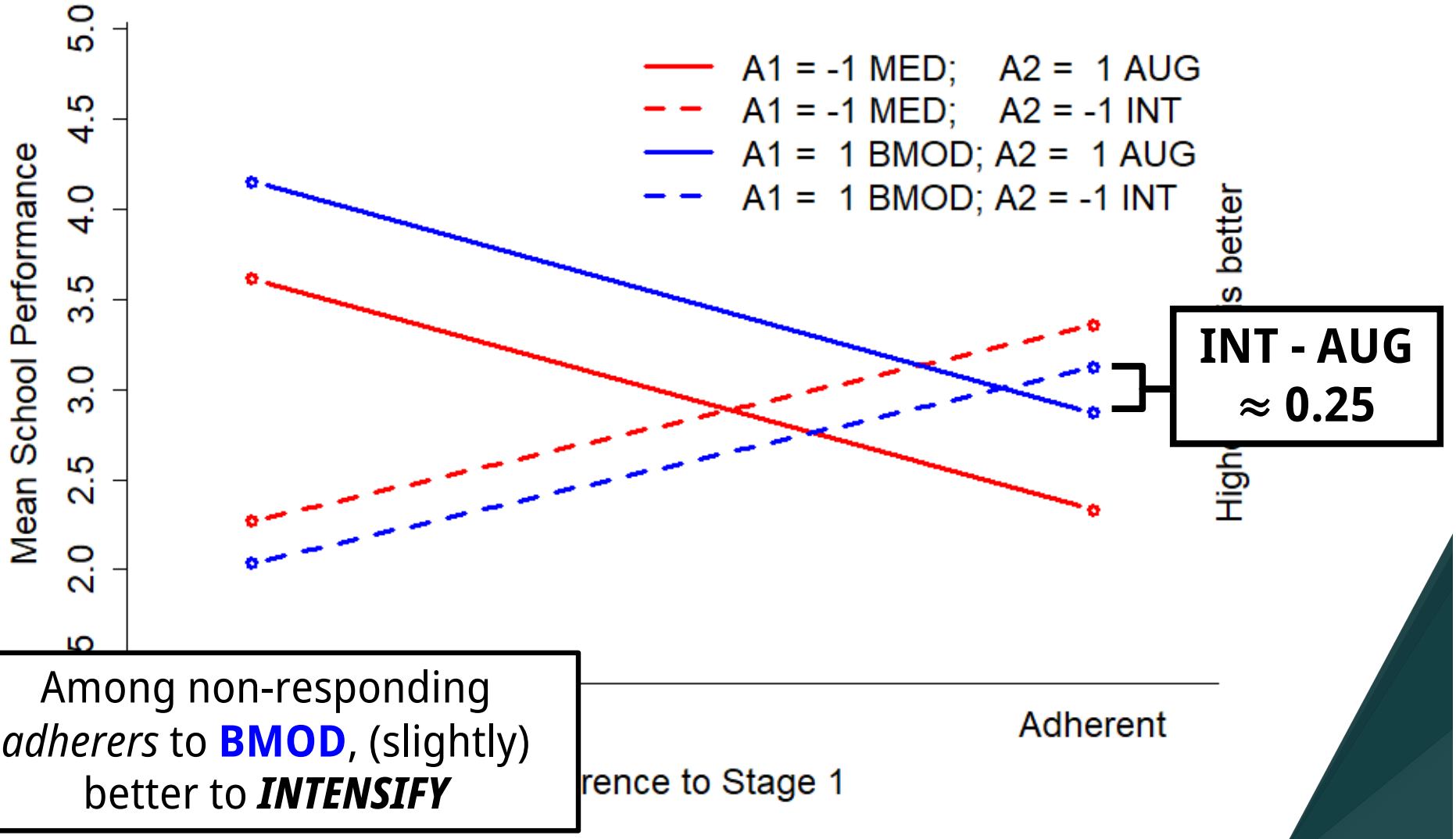


Among non-responding *adherers* to **MED**, better to ***INTENSIFY***

This analysis is with simulated data.

Step 1: Second-stage tailoring



Among non-responding *adherers* to **BMOD**, (slightly) better to ***INTENSIFY***

This analysis is with simulated data.

Step 2: Predicted outcome under the best stage 2 option

Next, we assign each non-responder the value $\widehat{Y}_i$

$\widehat{Y}_i$ = The expected outcome if each non-responder received **the best second-stage tactic** given their **initial treatment** and **adherence**

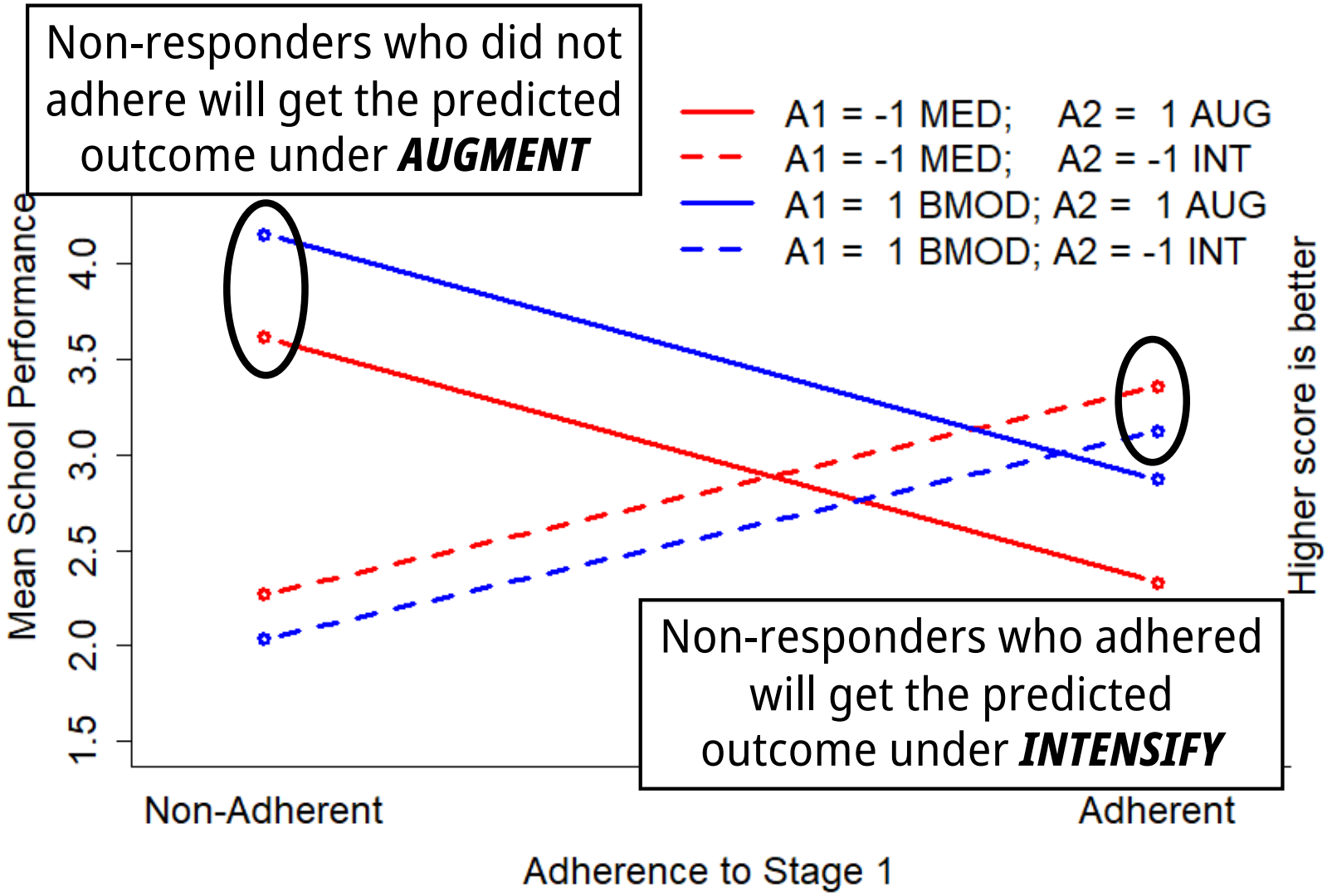
Step 2: Predicted outcome under the best stage 2 option

Next, we assign each non-responder the value $\widehat{Y}_i$

$\widehat{Y}_i$ = The expected outcome if each non-responder received **the best second-stage tactic** given their **initial treatment** and **adherence**

- We used Step 1 Regression to identify the best Stage 2 tactic for any given level of the tailoring variables.
- We use these results to estimate what the outcome for each non-responder if they received the best Stage 2 tactic, *given their observed values* on the tailoring variables
  - Given his/her observed values on the tailoring variables
- Responders? $\widehat{Y}_i = Y_i$

Step 2: Predicted outcome under the best stage 2 option



This analysis is with simulated data.

Step 2: Predicted outcome under the best stage 2 option

$$E[\,Y \mid O_1, A_1, O_2, A_2\,] = \beta_0 + \cdots + \beta_7 \boldsymbol{A_1} + \beta_8 \text{adherence} + \beta_9 A_2 + \beta_{10}(A_2 \times \boldsymbol{A_1}) + \beta_{11}(A_2 \times \text{adherence})$$

PRETEND FOR A MOMENT THAT:

$\beta_0 = 3,$ $\beta_6 = 0.1,$ $\beta_7 = -0.1,$ $\beta_8 = -1,$ $\beta_9 = -0.2,$ $\beta_{10} = 1.2$

Step 2: Predicted outcome under the best stage 2 option

$$E[\,Y \mid O_1, A_1, O_2, A_2\,] = \beta_0 + \cdots + \beta_7 \boldsymbol{A_1} + \beta_8 \text{adherence} + \beta_9 A_2 + \beta_{10}(A_2 \times \boldsymbol{A_1}) + \beta_{11}(A_2 \times \text{adherence})$$

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John was a non-responding, non-adhering (adherence=0) participant who received:
Stage 1: MED (A1 = 1)
Stage 2: INT (A2 = -1)
and had mean values for all baseline variables

Step 2: Predicted outcome under the best stage 2 option

$$E[\,Y \mid O_1, A_1, O_2, A_2\,] = \beta_0 + \cdots + \beta_7 \boldsymbol{A_1} + \beta_8 \text{adherence} + \beta_9 A_2 + \beta_{10}(A_2 \times \boldsymbol{A_1}) + \beta_{11}(A_2 \times \text{adherence})$$

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John was a non-responding, non-adhering (adherence=0) participant who received:
Stage 1: MED (A1 = 1)
Stage 2: INT (A2 = -1)
and had mean values for all baseline variables

$$\hat{Y} = 3 + 0.1(A_1) - 0.1(\text{adherence}) - 0.1(A_2) - 0.2(A_2 \times A_1) + 1.2(A_2 \times 0)$$

$$\hat{Y}_{A2=INT} = 3 + 0.1(1) - 0.1(0) - 0.1(1) - 0.2(1 \times 1) + 1.2(1 \times 0) = 2.8$$

John's score under INT (which he received)

$$\hat{Y}_{A2=AUG} = 3 + 0.1(1) - 0.1(0) - 0.1(-1) - 0.2(-1 \times 1) + 1.2(-1 \times 0) = 3.4$$

John's score under AUG (which he did not receive)

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Step 2: Predicted outcome under the best stage 2 option

$$E[\,Y \mid O_1, A_1, O_2, A_2\,] = \beta_0 + \cdots + \beta_7 \boldsymbol{A_1} + \beta_8 \text{adherence} + \beta_9 A_2 + \beta_{10}(A_2 \times \boldsymbol{A_1}) + \beta_{11}(A_2 \times \text{adherence})$$

PRETEND FOR A MOMENT THAT:

$$\beta_0 = 3, \quad \beta_6 = 0.1, \quad \beta_7 = -0.1, \quad \beta_8 = -1, \quad \beta_9 = -0.2, \quad \beta_{10} = 1.2$$

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John's score under INT (which he received)

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John's $\hat{Y}_i$

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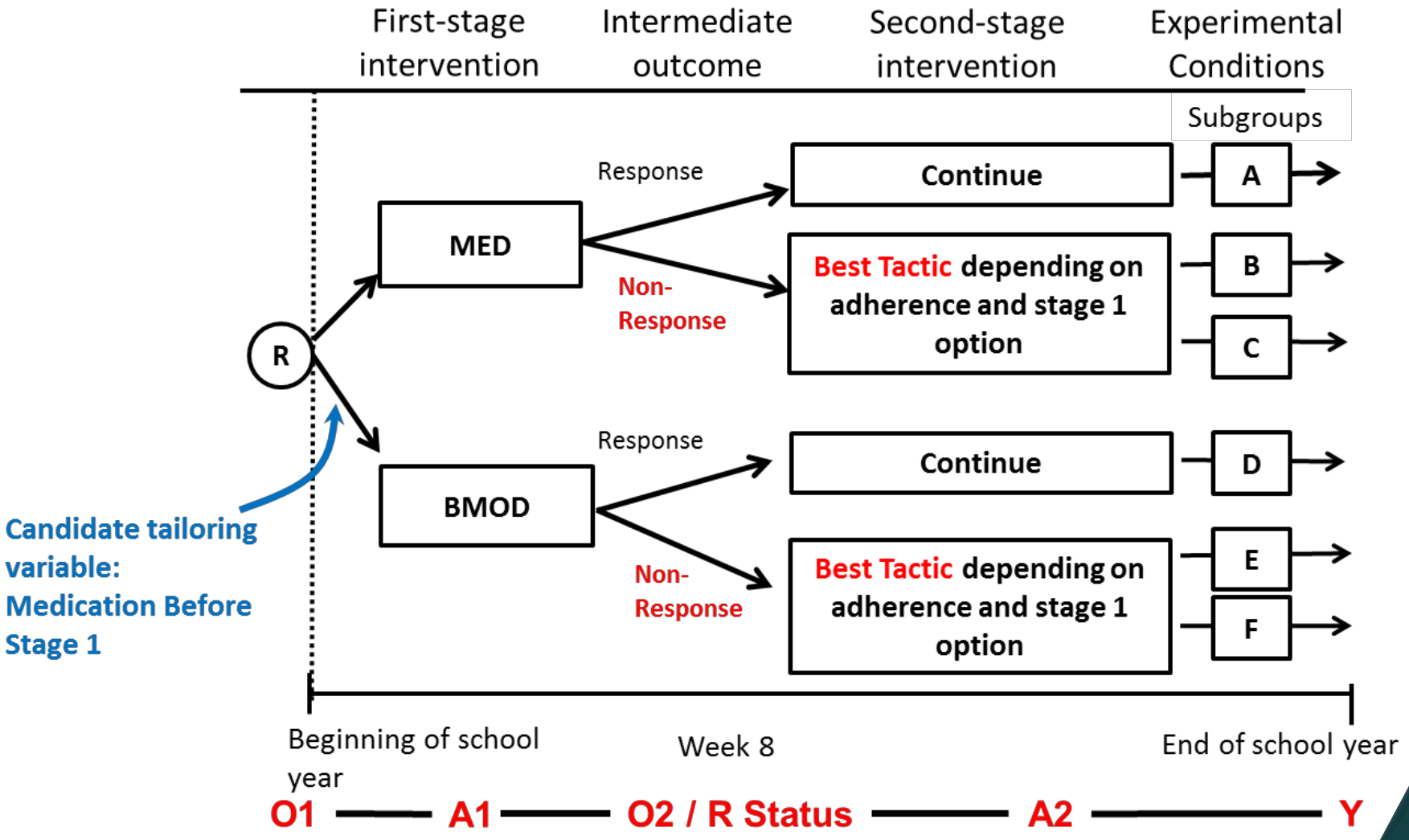
Step 3: Move backwards to first-stage tailoring



Step 3: Move backwards to first-stage tailoring

In this step, we seek to address the following question:

- Can we use information about **medication in prior year** to select the *best first-stage option*?
    - Assuming that in the future, non-responders get the best Stage 2 tactic

Step 3: Move backwards to first-stage tailoring

In this step, we seek to address the following question:

- Can we use information about **medication in prior year** to select the *best first-stage option*?
    - Assuming that in the future, non-responders get the best Stage 2 tactic
- We do this by using $\hat{Y}_i$ as the outcome in a regression where we explore the usefulness of **prior medication** for making decisions about *first-stage options*.

Step 3: Move backwards to first-stage tailoring

Fit the following regression model:

$$E\left[\hat{Y} \mid O_1, A_1\right] = \beta_0 + \beta_1 O_{11c} + \beta_2 O_{12c} + \beta_3 O_{14c} + \beta_4 \textbf{priorMed} + \beta_5 A_1 + \beta_6 (\textbf{priorMed} \times A_1)$$

Controlling for stage 2 tactic

Step 3: Move backwards to first-stage tailoring

Fit the following regression model:

$$E\left[\hat{Y} \mid O_1, A_1\right] = \beta_0 + \beta_1 O_{11c} + \beta_2 O_{12c} + \beta_3 O_{14c} + \beta_4 \textbf{priorMed} + \beta_5 A_1 + \beta_6 (\textbf{priorMed} \times A_1)$$

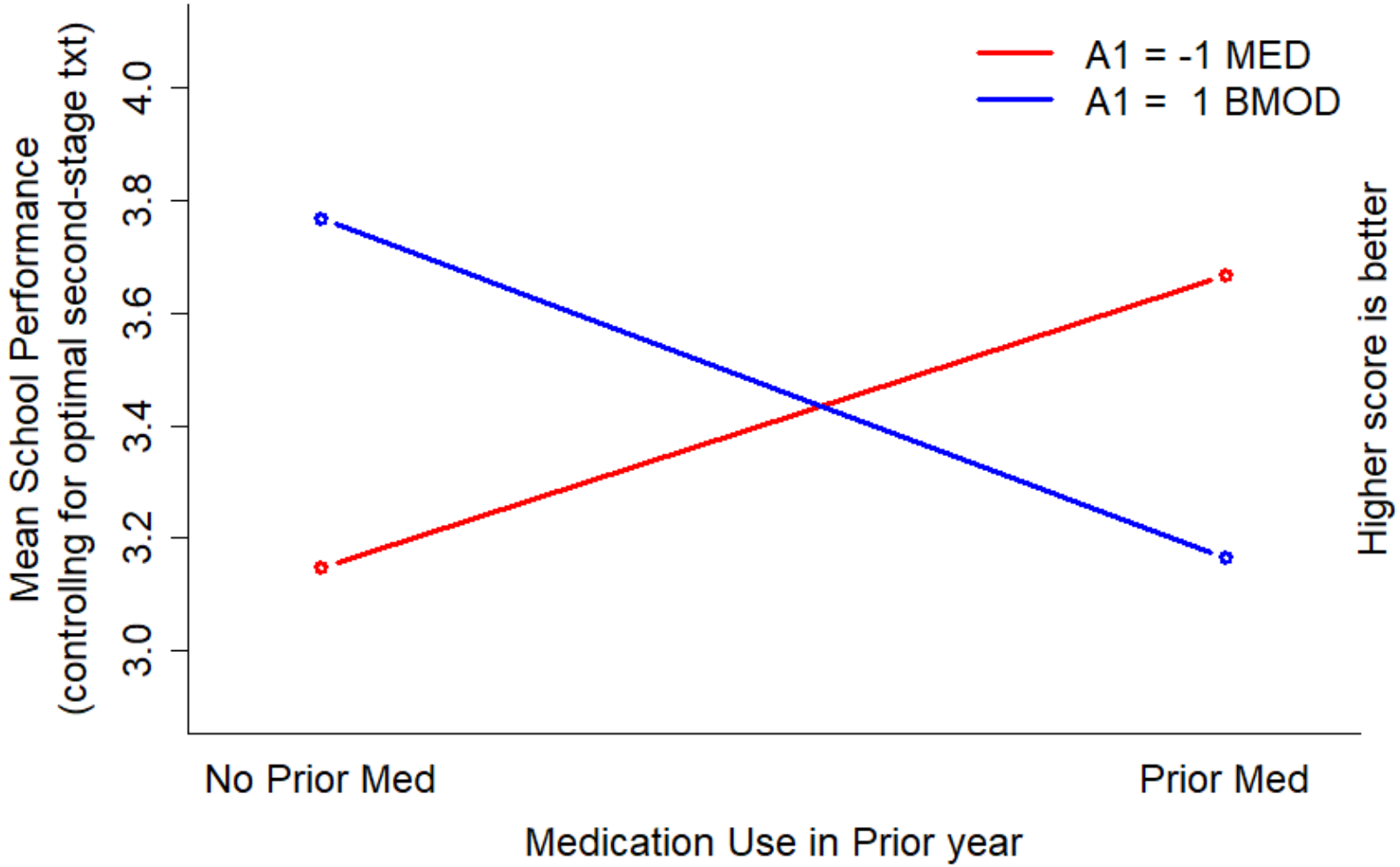
Controlling for stage 2 tactic

This model will help us to:

a) *Determine whether* the best first stage option varies depending on whether the child received medication in prior year; and

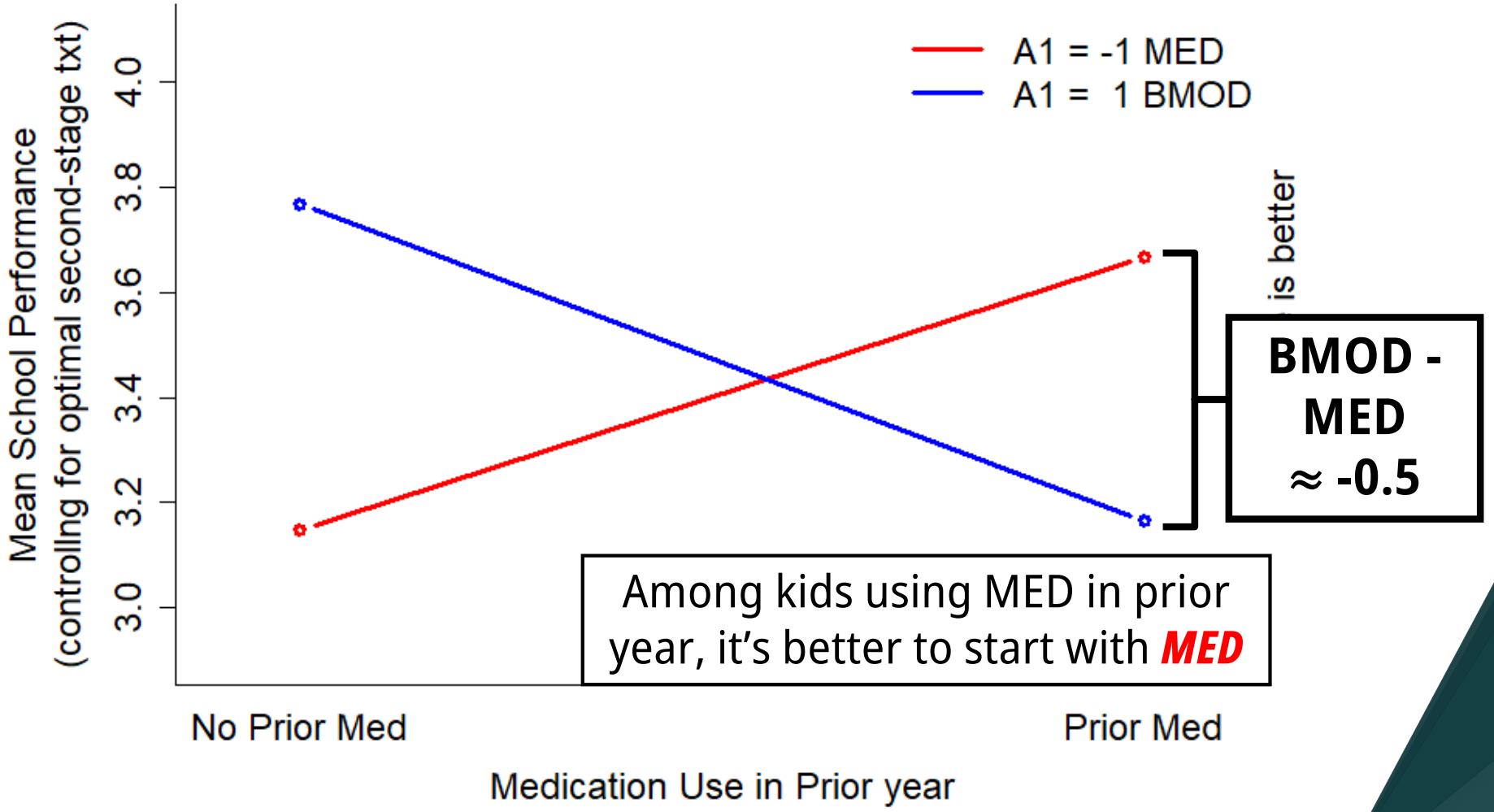
b) *Identify the best first stage option* for children who received med in prior year vs. those that did not.

Step 3: Move backwards to first-stage tailoring



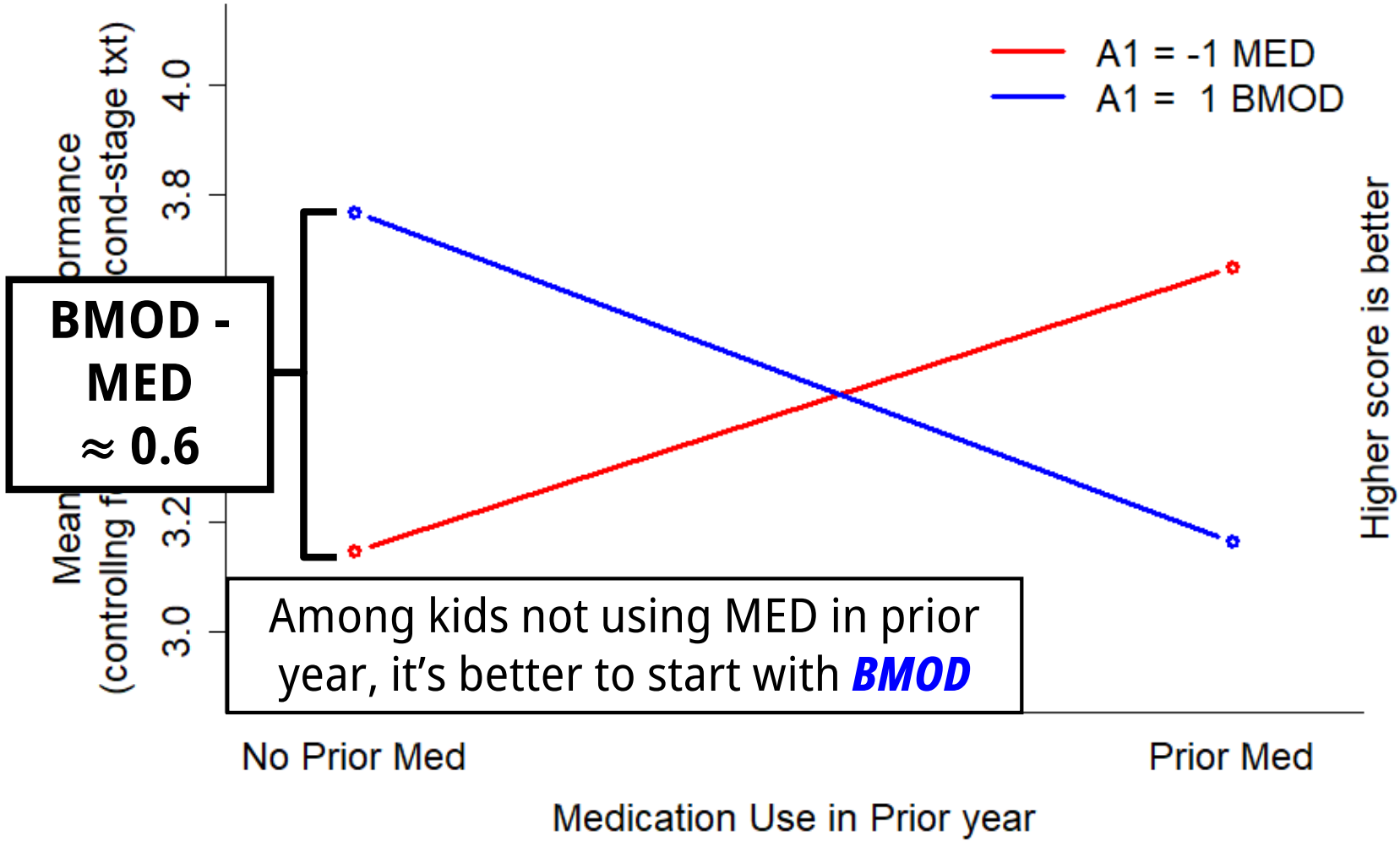
This analysis is with simulated data.

Step 3: Move backwards to first-stage tailoring



This analysis is with simulated data.

Step 3: Move backwards to first-stage tailoring



This analysis is with simulated data.

Summary of Q-learning results

Step 1

- ***Second-Stage Regression***
  - Are **O1, A1, and O2** useful in making decisions about second-stage tactics?
  - (Are **O1, A1, and O2** useful in deciding **which NR** would benefit from Augment vs. Intensify?)

Step 2

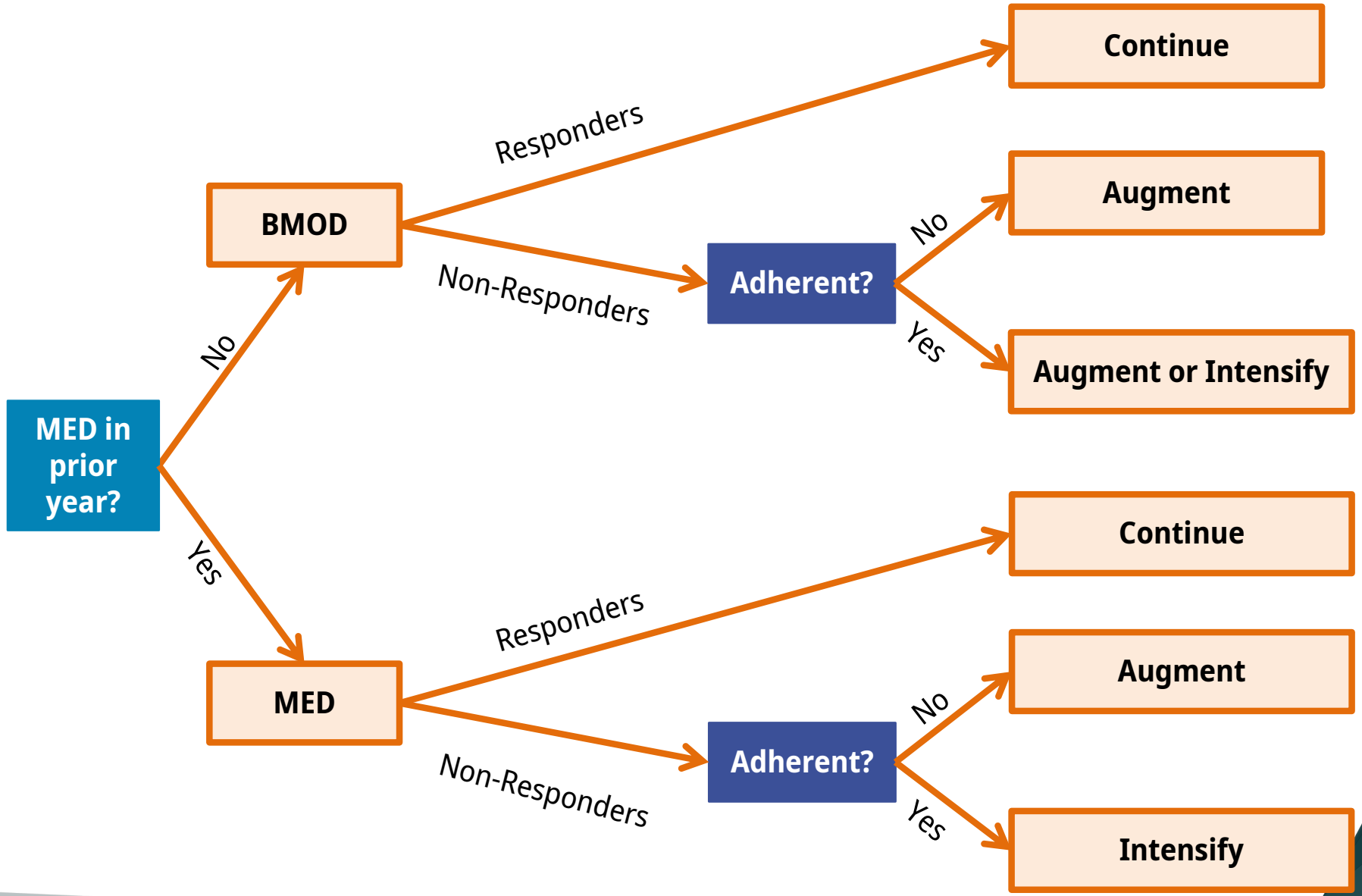
- ***Calculate*** $\hat{Y}_i$
  - What would the outcome be if they had received the best second-stage tactic given **O1, A1, and O2?**
  - **$\hat{Y}_i$ is the estimated optimal outcome under the best second-stage tactic for non-responders.** ($\hat{Y}_i$=Y for responders)

Step 3

- ***First-Stage Regression***
  - Is **O1** useful in making decisions about first-stage tactics, *assuming we use optimal second-stage tactic*? (Use **$\hat{Y}_i$** from Step 2 as the outcome!)
  - (Is **O1** useful in deciding who would benefit from MED vs. BMOD, *assuming NRs get the best second-stage treatment*?)

d³lab

The estimated more-deeply tailored AI is



The estimated more-deeply tailored AI is

At the beginning of school year

IF **medication in prior year** = {NO}

THEN stage 1 = {BMOD}.

ELSE IF **medication in prior year** ={YES}

THEN stage 1 = {MED}

Then, every month,

beginning at week 8…

The estimated more deeply-tailored AI is

... *Then, every month,*
beginning at week 8

IF **response status** to Stage 1 = {NR}
THEN
IF **adherence** to MED or BMOD= {NO},
THEN Stage 2 = {AUGMENT}.
ELSE IF **adherence** to MED = {YES},
THEN Stage 2 = {INTENSIFY}.
ELSE IF **adherence** to BMOD = {YES},
THEN Stage 2 = {AUGMENT} or {INTENSIFY}.
ELSE IF **response status** to Stage 1 = {R}
THEN CONTINUE Stage 1.

Preview of SAS code for Q-learning

What you can do:

- Step 1 using regression
- Steps 2 and 3 using a SAS add-on known as PROC QLEARN

Here's a quick preview of how to use these tools.

SAS code for Q-learning

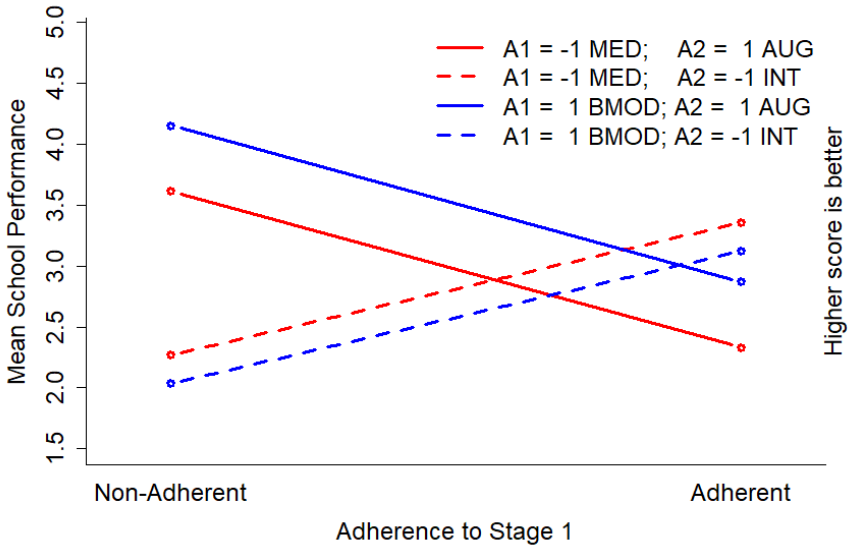
Second-Stage Regression:

$$E[Y \mid .. O_2, A_2] = \beta_0 + \beta_1 O_{11c} + \beta_2 O_{12c} + \beta_3 O_{13c} + \beta_4 O_{14c} + \beta_5 O_{12c} + \beta_6 O_{21c} + \beta_7 \boldsymbol{A_1} + \beta_8 \boldsymbol{O_{22}} + \beta_9 A_2 + \beta_{10}(A_2 \times \boldsymbol{A_1}) + \beta_{11}(A_2 \times \boldsymbol{O_{22}})$$

```
* Use only non-responders;
data dat10; set dat1; if R=0; run;

proc genmod data = dat10;
  model y = o11cnr o12cnr o13cnr o14cnr o21cnr  a1   o22   a2 a2*a1 a2*o22;
  * INTENSIFY vs. AUGMENT when Stage 1 = MED, by ADHERENCE status;
  estimate 'Diff: INT vs AUG for NR ADH MED'      a2  2 a2*a1 -2 a2*o22  2 ;
  estimate 'Diff: INT vs AUG for NR Non-ADH MED'  a2  2 a2*a1 -2 a2*o22  0 ;
  * INTENSIFY vs. AUGMENT when Stage 1 = BMOD, by ADHERENCE status;
  estimate 'Diff: INT vs AUG for NR ADH BMOD'     a2  2 a2*a1  2 a2*o22  2 ;
  estimate 'Diff: INT vs AUG for NR Non-ADH BMOD' a2  2 a2*a1  2 a2*o22  0 ;
run;
```

Step 1 results of Q-learning



Contrast Estimate Results

Label	Mean Estimate	95% Confidence Limits		Standard Error	Pr > ChiSq
		Lower	Upper		
Diff: INT vs AUG for NR ADH MED	**1.0240**	0.4131	1.6350	0.3117	**0.0010**
Diff: INT vs AUG for NR Non-ADH MED	**-1.3412**	-1.9896	-0.6927	0.3308	**<.0001**
Diff: INT vs AUG for NR ADH BMOD	**0.2503**	-0.3950	0.8956	0.3292	**0.4471**
Diff: INT vs AUG for NR Non-ADH BMOD	**-2.1149**	-2.7050	-1.5248	0.3011	**<.0001**

What does PROC QLEARN provide?

1. Data set with O1, A1, R, O2, A2, Y

2. The first regression model (best Stage 2 tactic)

$$Y \sim O1, A1, O2, A2$$

NB: Be sure to specify sub-sample for this regression (non-responders in ADHD SMART)

3. The second regression model (best Stage 1 option)

$$\hat{Y} \sim O1, A1$$

Preview of Code for PROC QLEARN

Model Specification

```
PROC QLEARN <options for input> ;
   MAIN1 variables;
   TAILOR1 variables;
   MAIN2 variables;
   TAILOR2 variables;
   RESPONSE variable;
   STG1TRT variable;     *Must be coded -1/+1
   STG2TRT variable;     *Must be coded -1/+1
   STG2SAMPLE variable;  *0/1 indicator specifying sample used for Stage 2
   ALPHA value;          *Type-I error to calculate CI for Stage 1 regression
RUN;
```

Regression 1 (Stage 2):

```
INT + MAIN2 + TAILOR2 + TAILOR2*STG2TRT + STG2TRT
```

Regression 2 (Stage 1):

```
INT + MAIN1 + TAILOR1 + TAILOR1*STG1TRT + STG1TRT
```

What we learned from Q-learning

At the beginning of school year

IF **medication in prior year** = {NO}

THEN stage 1 = {BMOD}.

ELSE IF **medication in prior year** ={YES}

THEN stage 1 = {MED}

Then, every month,

beginning at week 8…

What we learned from Q-learning

... *Then, every month,*
beginning at week 8

IF **response status** to Stage 1 = {NR}
THEN
IF **adherence** to MED or BMOD= {NO},
THEN Stage 2 = {AUGMENT}.
ELSE IF **adherence** to MED = {YES},
THEN Stage 2 = {INTENSIFY}.
ELSE IF **adherence** to BMOD = {YES},
THEN Stage 2 = {AUGMENT} or {INTENSIFY}.

ELSE IF **response status** to Stage 1 = {R}
THEN CONTINUE Stage 1.

What we learned from Q-learning

The **mean Y**, school performance, **under the more deeply tailored AI** obtained via Q-learning is estimated to be **3.72**.

- Recall (BMOD, AUGMENT) was the AI with the largest mean among the 4 embedded AIs (only tailored on response)
- The value of the more deeply-tailored AI is larger than the value of the AI that started with BMOD and used AUGMENT for non-responders (mean = **3.51**)

What we learned from Q-learning

We may want to evaluate the efficacy of this ***proposed AI*** versus a suitable control (e.g., usual care) with a subsequent trial (i.e., RCT)

References

Nahum-Shani, I., Qian, M., Almirall, D., Pelham, W. E., Gnagy, B., Fabiano, G. A., ... & Murphy, S. A. (2012). Q-learning: A data analysis method for constructing adaptive interventions. Psychological methods, 17(4), 478.