



Presented by
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Repeated Outcome Measures in SMARTs

Module 8



Overview

- In all previous modules, we have focused on analyzing a single outcome measured at the end of the SMART
- This module discusses the setting in which we collect related outcome measurements at multiple time points
- **Example.** Academic performance during the course of the school year



Outline

Overview of SMART designs with repeated outcome measures

Common scientific questions you can answer with repeated outcome measures

Data analysis methods for repeated outcome measures

Sample size considerations for planning SMARTs with repeated outcome measures



Outline

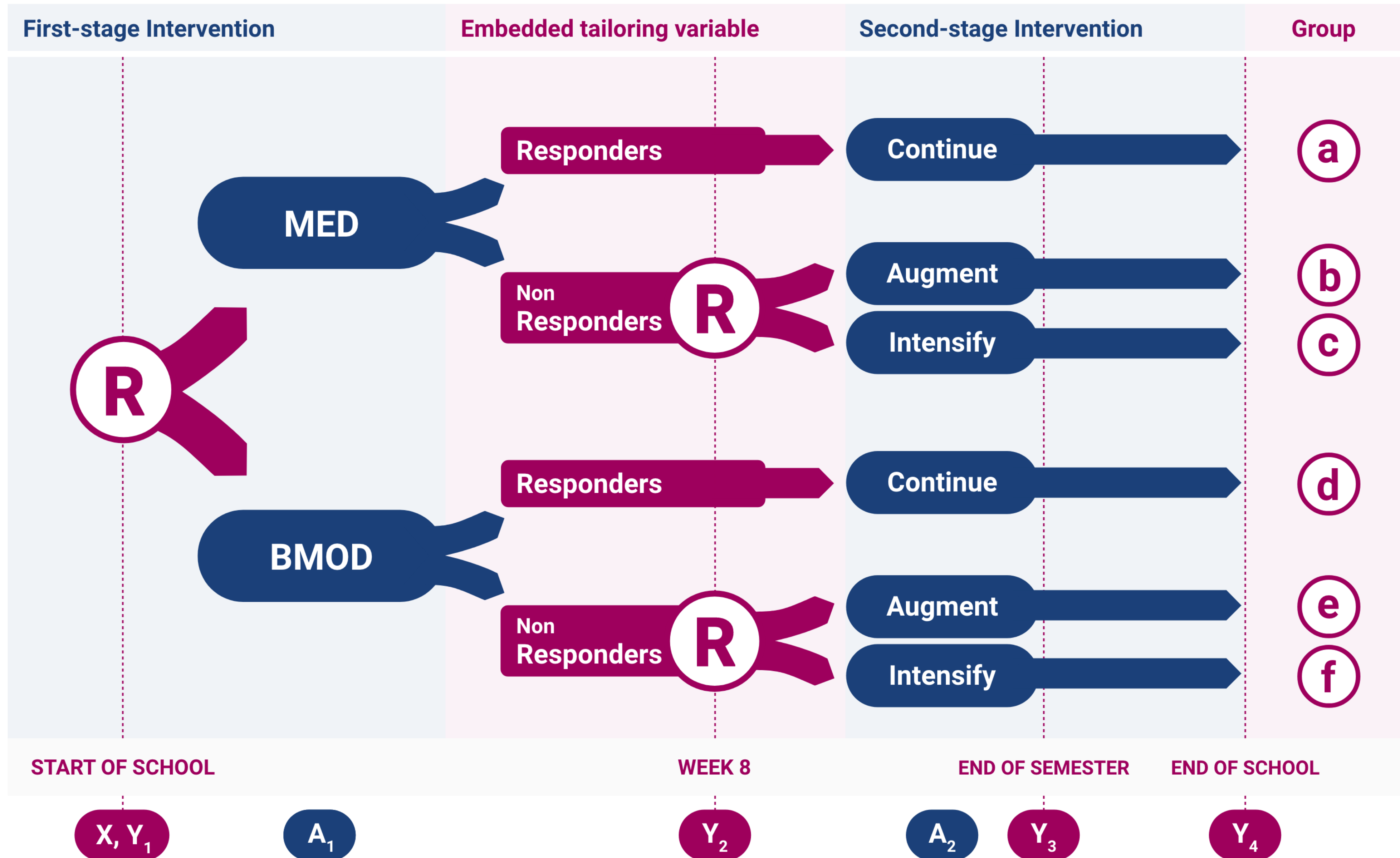
Overview of SMART designs with repeated outcome measures

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4 Adaptive Interventions Embedded in the ADHD SMART

Expressed as if-then statements

Embedded AI 1

Stage 1 = {MED};
if response status = {NR},
then, Stage 2 = {AUGMENT};
else if response status = {R},
then, Continue Stage 1

Embedded AI 3

Stage 1 = {MED};
if response status = {NR},
then, Stage 2 = {INTENSIFY};
else if response status = {R},
then, Continue Stage 1

Embedded AI 2

Stage 1 = {BMOD};
if response status = {NR},
then, Stage 2 = {AUGMENT};
else if response status = {R},
then, Continue Stage 1

Embedded AI 4

Stage 1 = {BMOD};
if response status = {NR},
then, Stage 2 = {INTENSIFY};
else if response status = {R},
then, Continue Stage 1



Recall Typical Primary Aim 3

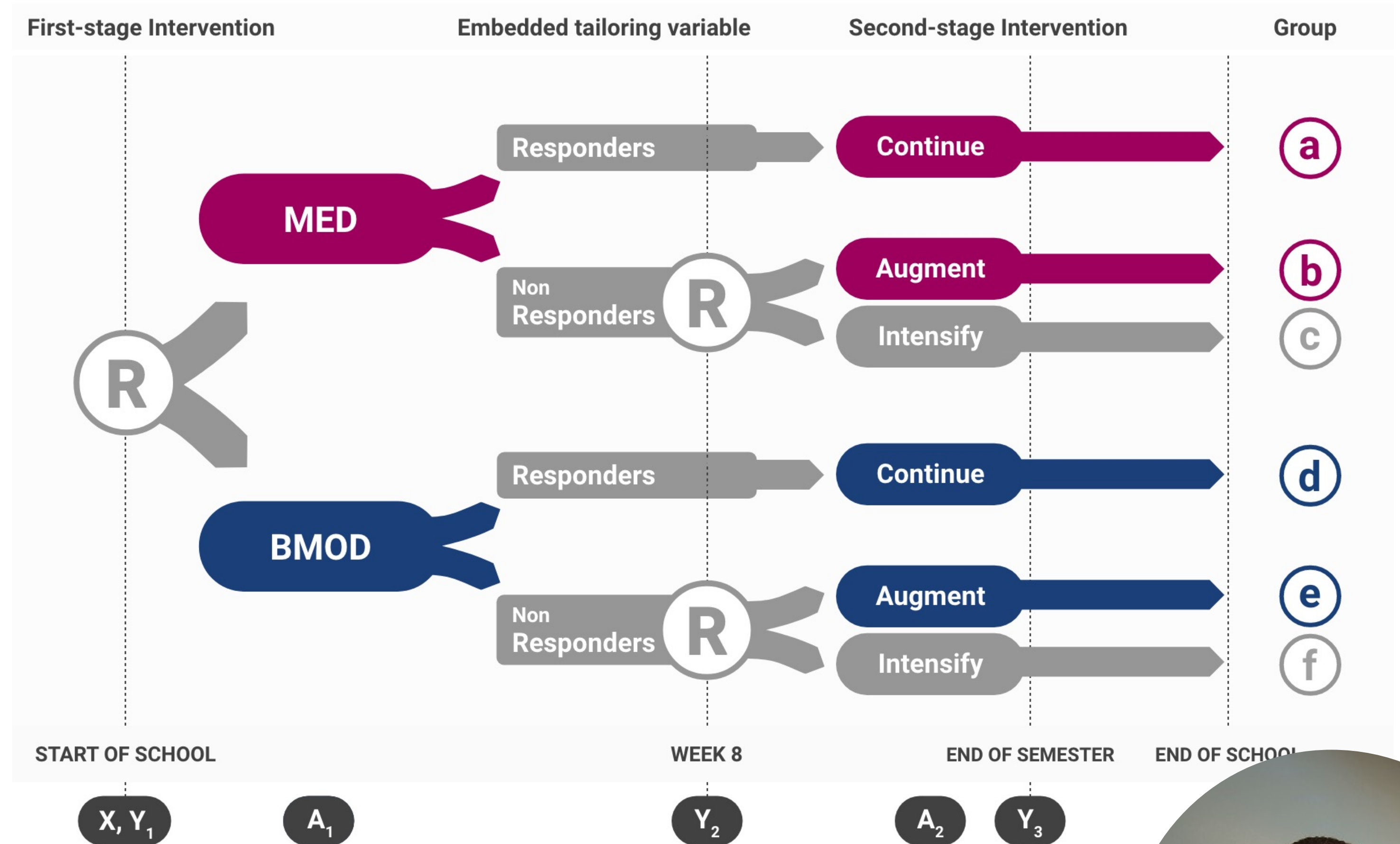
Compare 2 embedded AIs in terms of a single end-of-study outcome (Y_3 or Y_4)

Embedded AI 1

Stage 1 = {MED};
if response status = {NR},
then, Stage 2 = {AUGMENT};
else if response status = {R},
then, Continue Stage 1

Embedded AI 2

Stage 1 = {BMOD};
if response status = {NR},
then, Stage 2 = {AUGMENT};
else if response status = {R},
then, Continue Stage 1



Given repeated outcome measures, are there other ways in which we might compare these AIs?



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Variations on Aim Type 3 with Repeated Outcome Measures

Comparing embedded adaptive interventions in a SMART with repeated outcome measures involved measuring and comparing the following metrics between AIs.

- a. End-of-study outcomes
- b. Time-averaged outcomes (AUC)
- c. Outcome trajectories (delayed effects)



Variations on Aim Type 3 with Repeated Outcome Measures

Comparing embedded adaptive interventions in a SMART with repeated outcome measures involved measuring and comparing the following metrics between AIs.

- a. End-of-study outcomes
- b. Time-averaged outcomes (AUC)
- c. Outcome trajectories (delayed effects)
 - See Xi et al. 2015 for details



End-of-Study Outcomes

- **Scientific Question:** Is AI #1 better than AI #2 in terms of academic performance at the end of the school year?
- **Primary Aim:** Compare AI #1 and AI #2 in terms of academic performance at the end of the school year
- **Why** collect repeated outcome measures when I care about a single end point?
 - Collecting multiple outcomes can lead to **statistical efficiency gains** by effectively “de-noising” the outcome
 - We may have other **secondary/exploratory** aims that involve other time points



Time-averaged Outcomes (AUC)

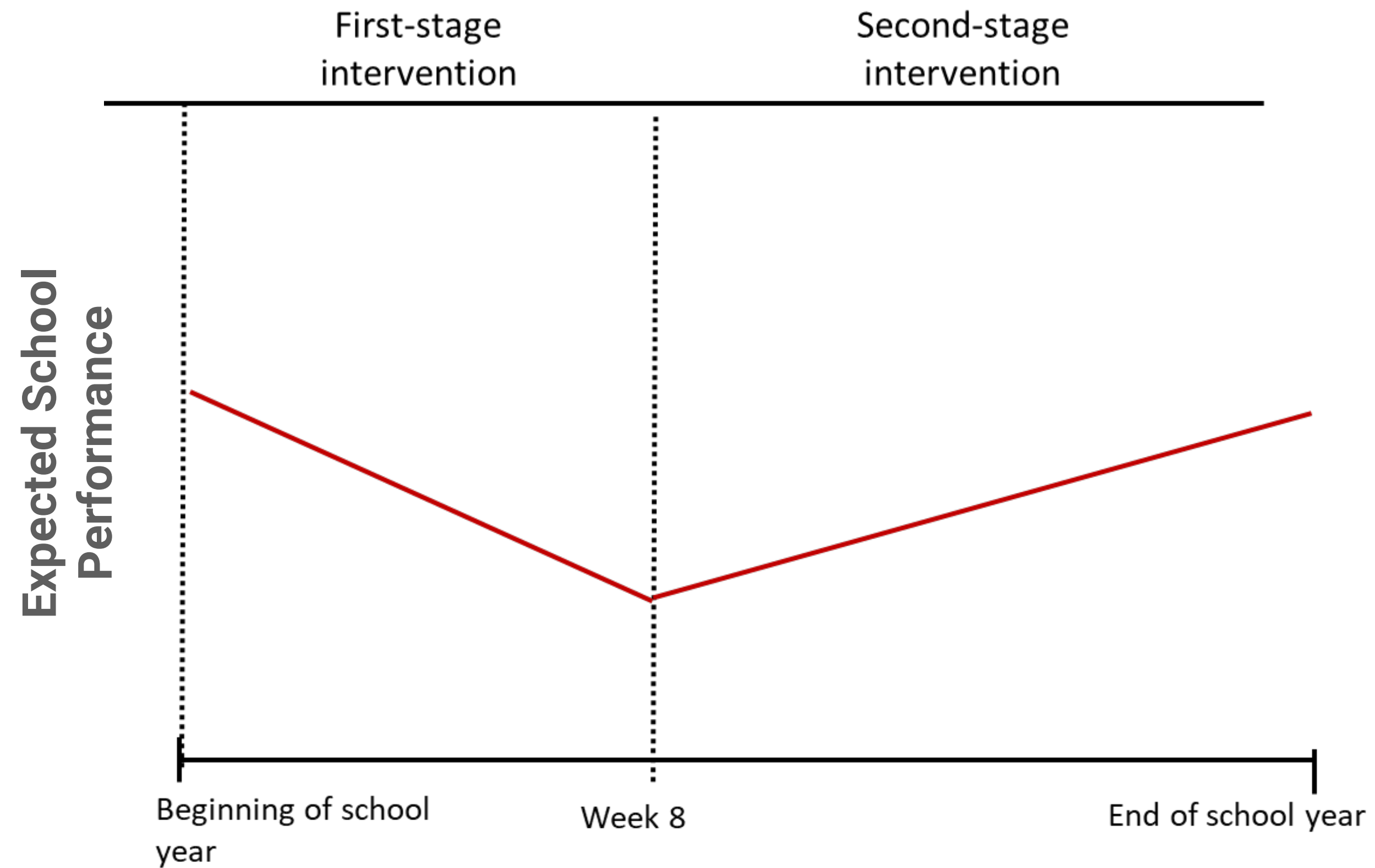
- **Scientific Question:** Is AI #1 better than AI #2 in terms of typical academic performance?
- **Primary Aim:** Compare AI #1 and AI #2 in terms of area-under-the-curve (AUC) for academic performance
- This primary aim is especially relevant when we would like to optimize the **typical value** of an outcome *over time* as opposed to a **single value** at a *specific point in time*
- For the ADHD study, AUC is a great choice because the goal is to improve student performance **throughout the school year**, not necessarily at a specific moment in time



Time-averaged Outcomes (AUC)

Area Under the Curve (AUC)

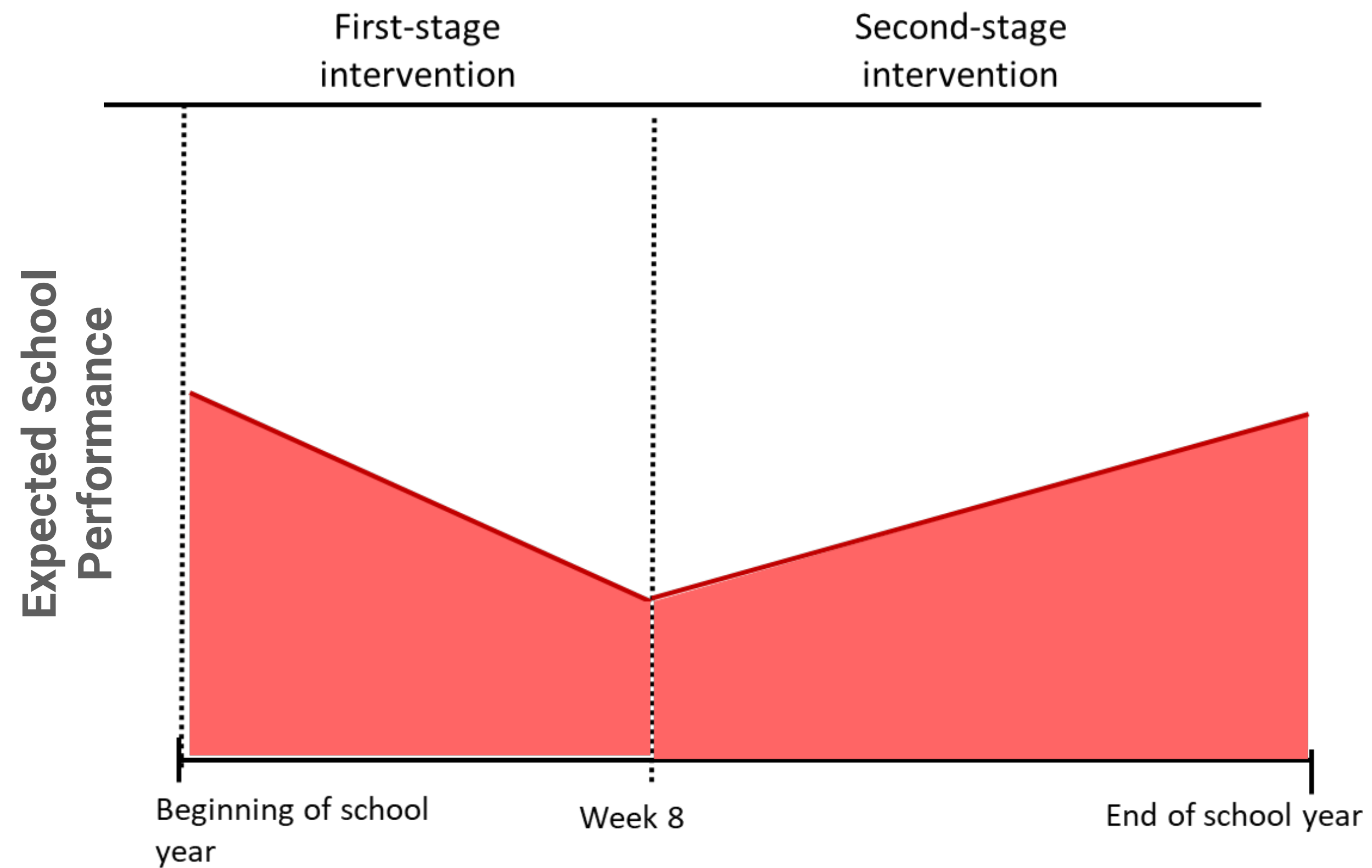
- AI #1 AUC



Time-averaged Outcomes (AUC)

Area Under the Curve (AUC)

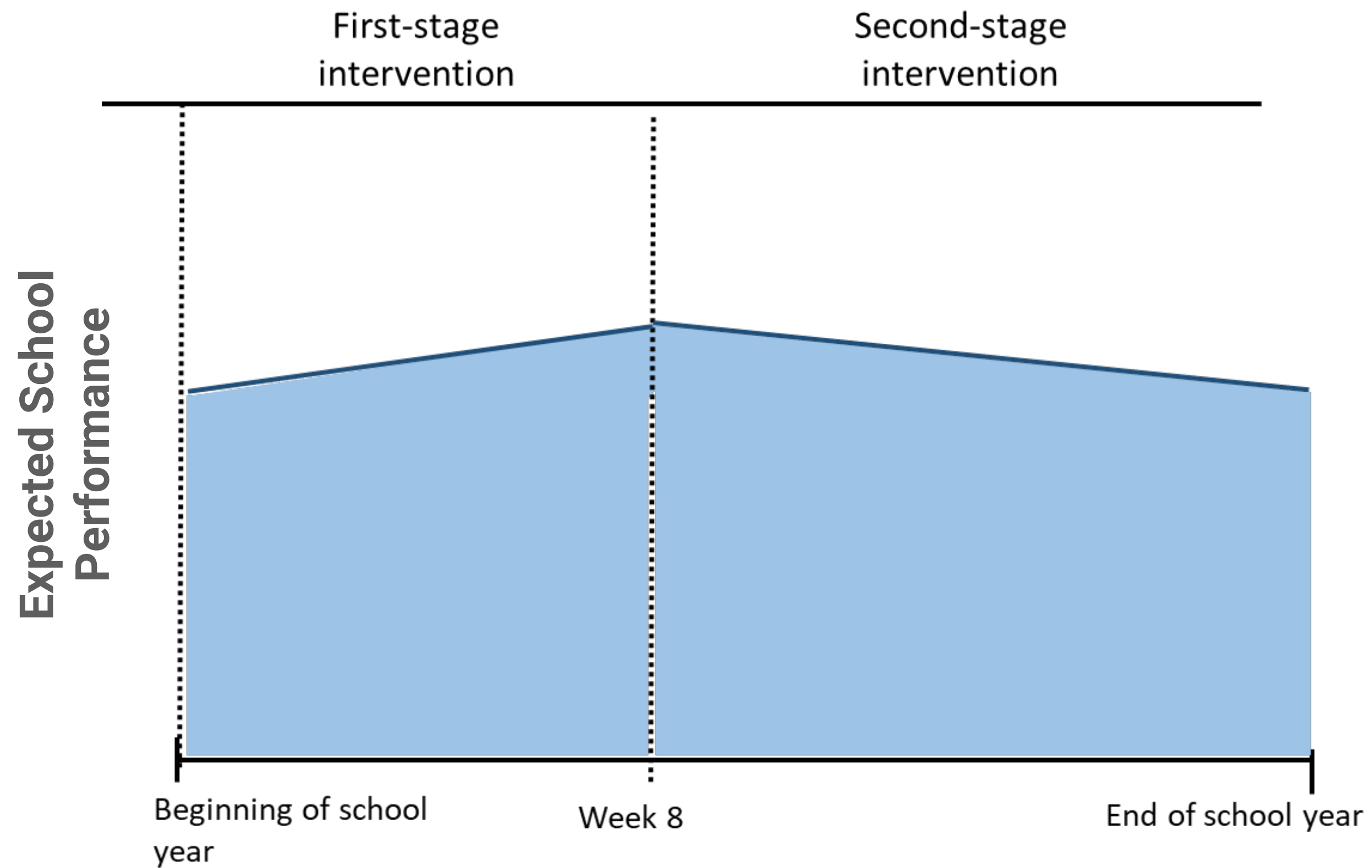
- AI #1 AUC



Time-averaged Outcomes (AUC)

Area Under the Curve (AUC)

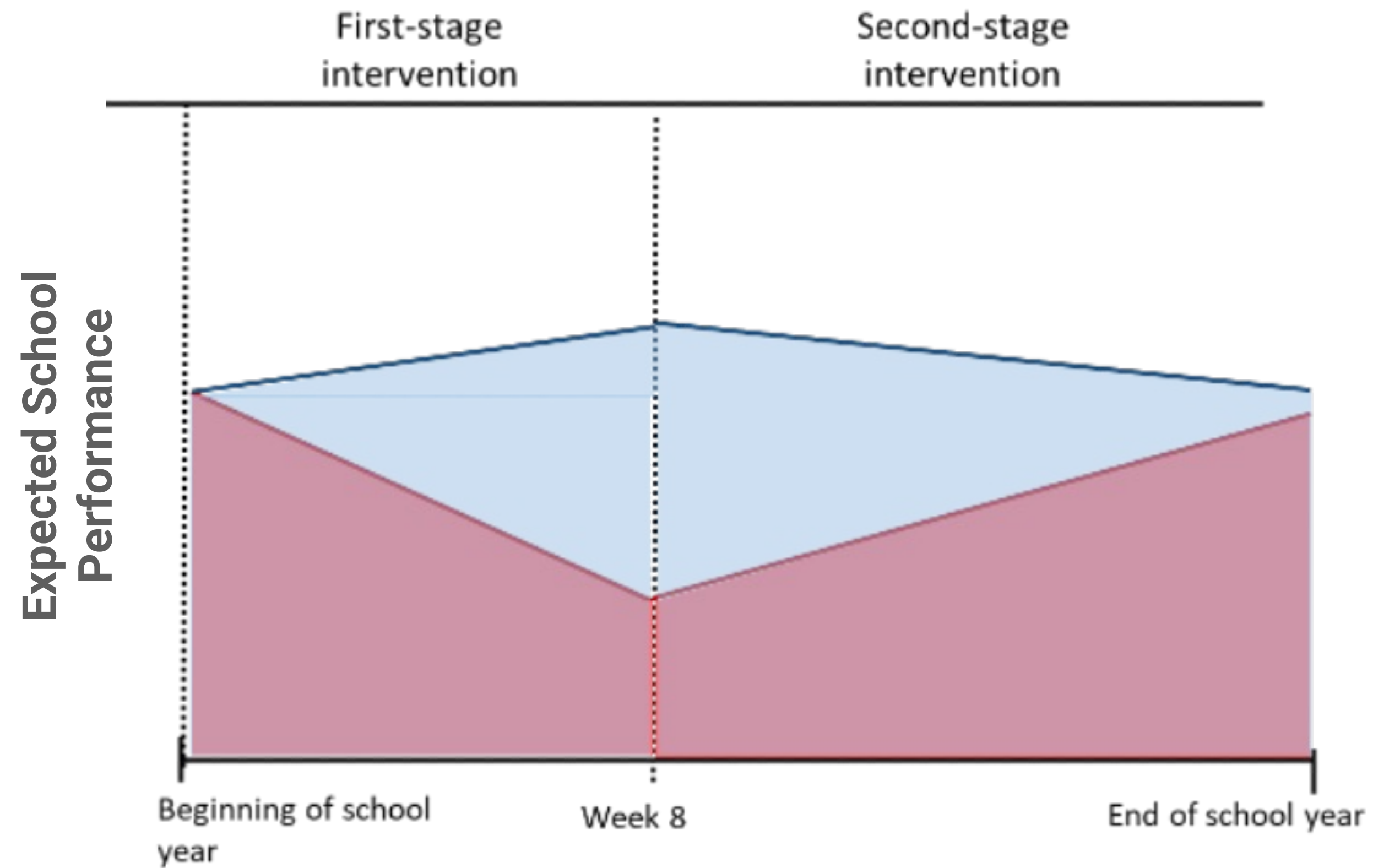
- AI #2 AUC



Time-averaged Outcomes (AUC)

Area Under the Curve (AUC)

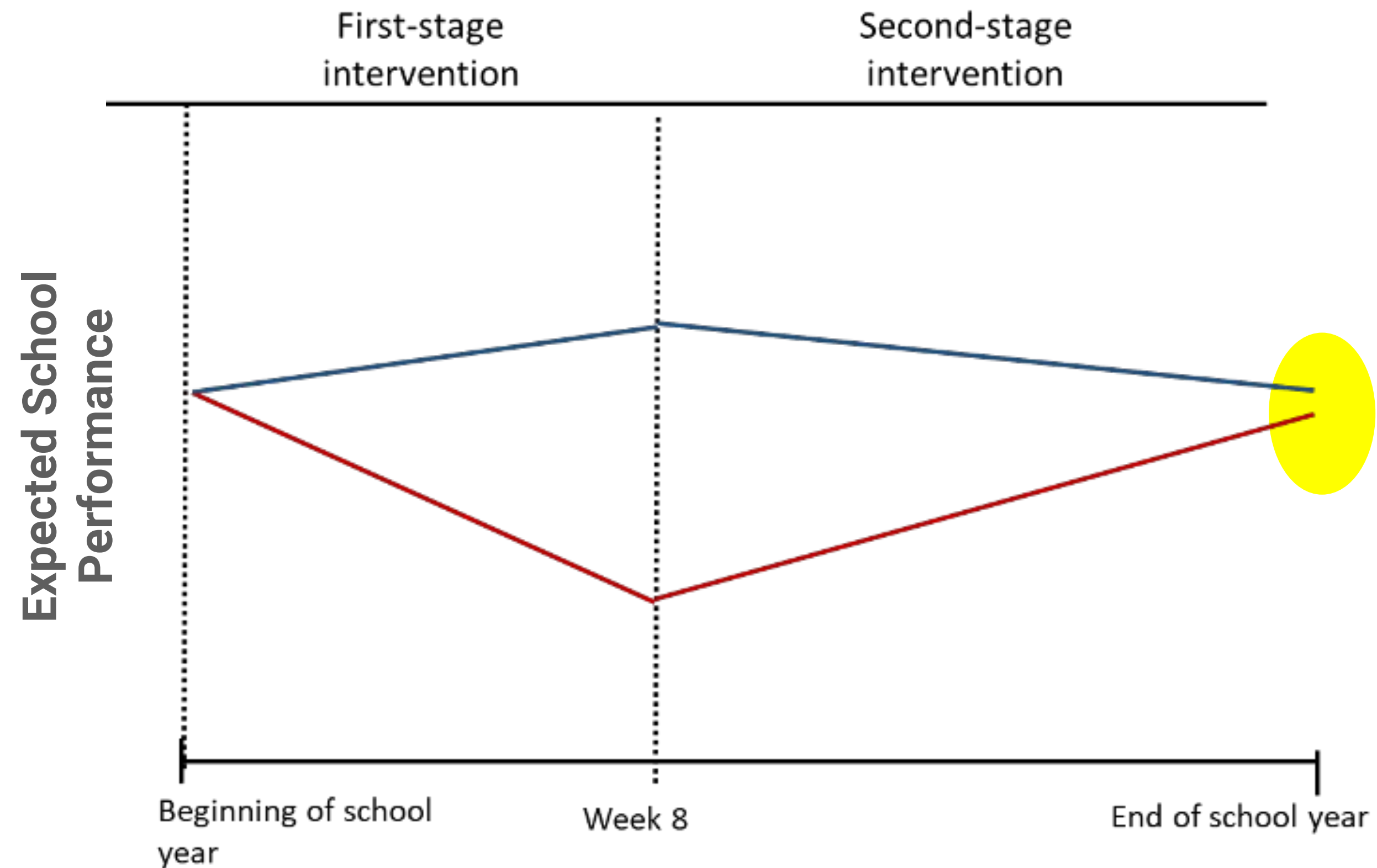
- Difference in AUC AI #1 – AI #2



Time-averaged Outcomes (AUC)

Area Under the Curve (AUC)

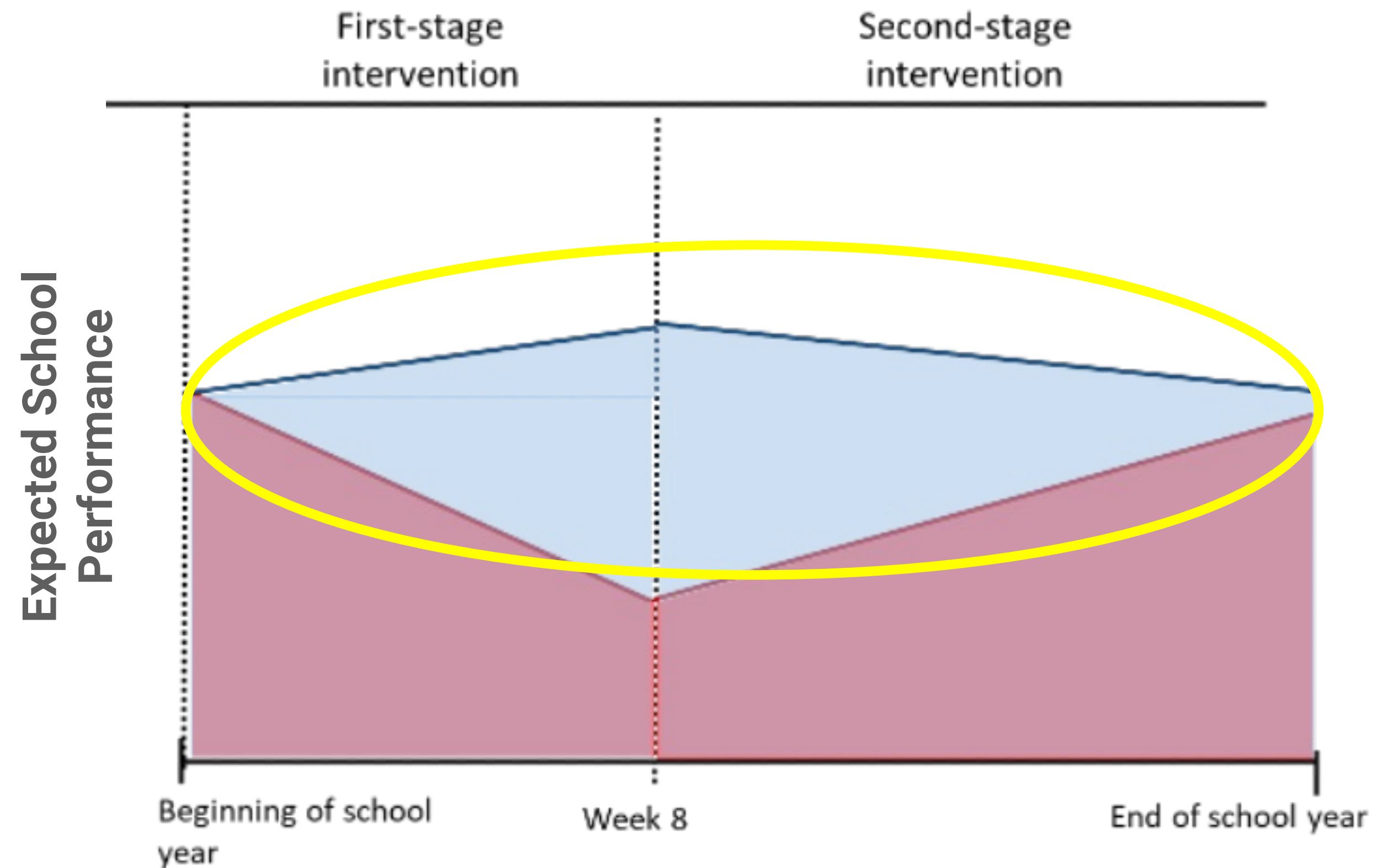
- If you compare the two adaptive interventions in terms of end-of-school year outcome, what would you conclude?



Time-averaged Outcomes (AUC)

Area Under the Curve (AUC)

- If you compare in terms of AUC...



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Overview of SMART designs with repeated outcome measures

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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

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



End of Study Primary Outcome Analysis Review

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

A_1	A_2
1 BMOD	1 INTENSIF Y
-1 MED	-1 AUGMENT

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



End of Study Primary Outcome Analysis Review

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

A_1	A_2
1 BMOD	1 INTENSIF Y
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$$E[Y|A_1, A_2] = \beta_0 + \beta_1 A_1 + \beta_2 A_2 + \beta_3 A_1 A_2$$



End of Study Primary Outcome Analysis Review

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

A_1	A_2
1 BMOD	1 INTENSIF Y
-1 MED	-1 AUGMEN T

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

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

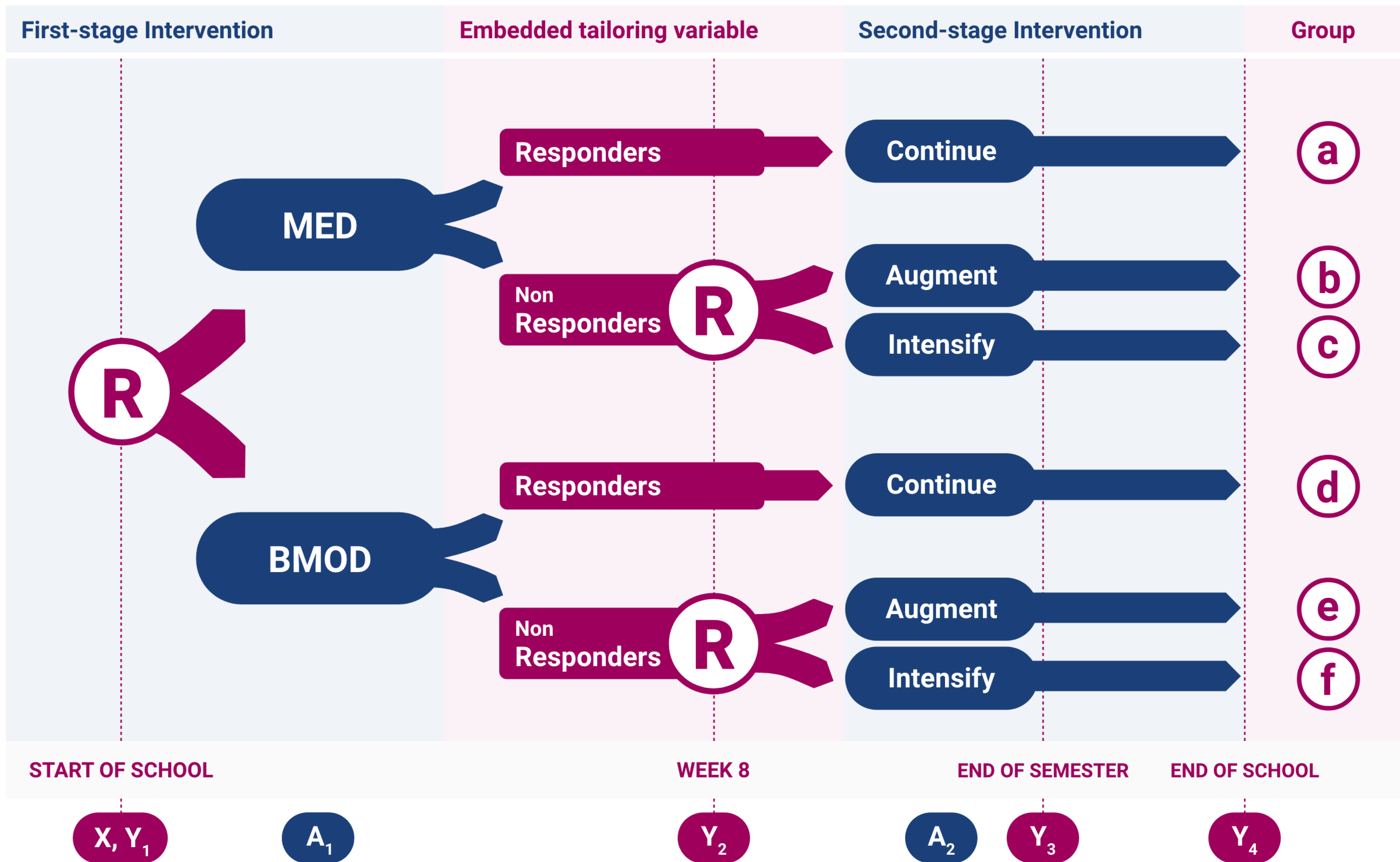
A_1	A_2
1 BMOD	1 INTENSIF Y
-1 MED	-1 AUGMENT

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

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

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





How can We Adapt This Strategy to Analyze a SMART with Repeated Outcome Measures?



Longitudinal Outcome Analysis

Step 1: Weight and replicate the data

Complication: We have multiple rows per individual

Solution: Replicate every row for responders



Longitudinal Outcome Analysis

Step 1: Weight and replicate the person-period data

Fake data would look like this:

<i>ID</i>	<i>Month</i>	<i>ODD at baseline</i>	<i>Response Status</i>	<i>School Perf</i>	<i>A1</i>	<i>A2</i>	<i>W</i>
<i>ID</i>	<i>t</i>	<i>O11</i>	<i>R</i>	<i>Y</i>	<i>A1</i>	<i>A2</i>	<i>W</i>
13	0	1	0	1	-1	1	4
13	2	1	0	5	-1	1	4
13	4	1	0	5	-1	1	4
13	8	1	0	3	-1	1	4
14	0	0	1	2	1	1	2
14	0	0	1	2	1	-1	2
14	2	0	1	5	1	1	2
14	2	0	1	5	1	-1	2
14	4	0	1	4	1	1	2
14	4	0	1	4	1	-1	2
14	8	0	1	5	1	1	2
14	8	0	1	5	1	-1	2



Longitudinal Outcome Analysis

Step 1: Weight and replicate the person-period data

Fake data would look like this:

	<i>Month</i>	<i>ODD at baseline</i>	<i>Response Status</i>	<i>School Perf</i>				
<i>ID</i>	<i>t</i>	<i>O11</i>	<i>R</i>	<i>Y</i>	<i>A1</i>	<i>A2</i>	<i>W</i>	
13	0	1	0	1	-1	1	4	
13	2	1	0	5	-1	1	4	
13	4	1	0	5	-1	1	4	
13	8	1	0	3	-1	1	4	
14	0	0	1	2	1	1	2	
14	0	0	1	2	1	-1	2	
14	2	0	1	5	1	1	2	
14	2	0	1	5	1	-1	2	
14	4	0	1	4	1	1	2	
14	4	0	1	4	1	-1	2	
14	8	0	1	5	1	1	2	
14	8	0	1	5	1	-1	2	



Longitudinal Outcome Analysis

Step 2: Select and fit a model

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

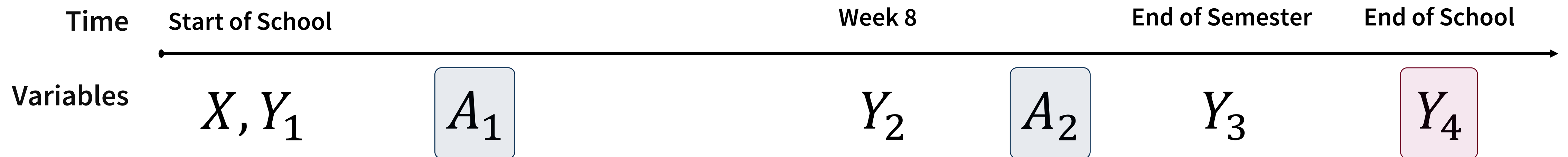
- This model is for a single end-of-study outcome
- But we can extend for additional repeated outcome measures



Longitudinal Outcome Analysis

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

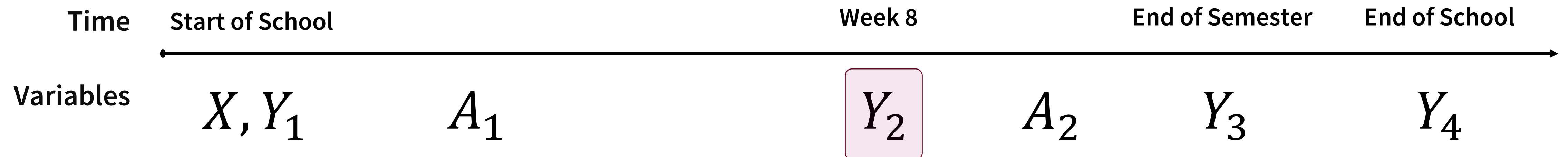
- The model we select should allow the outcome at each stage to be impacted only by intervention options that were offered prior to that stage.



Longitudinal Outcome Analysis

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

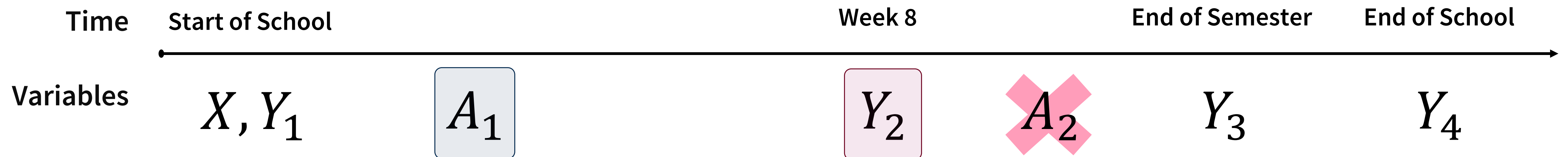
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Longitudinal Outcome Analysis

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

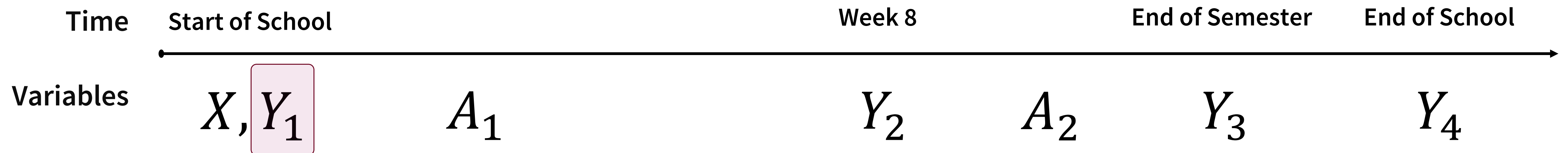
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Longitudinal Outcome Analysis

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

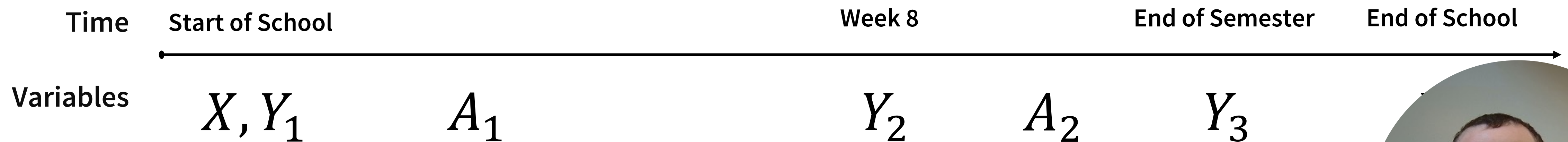
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Longitudinal Outcome Analysis

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

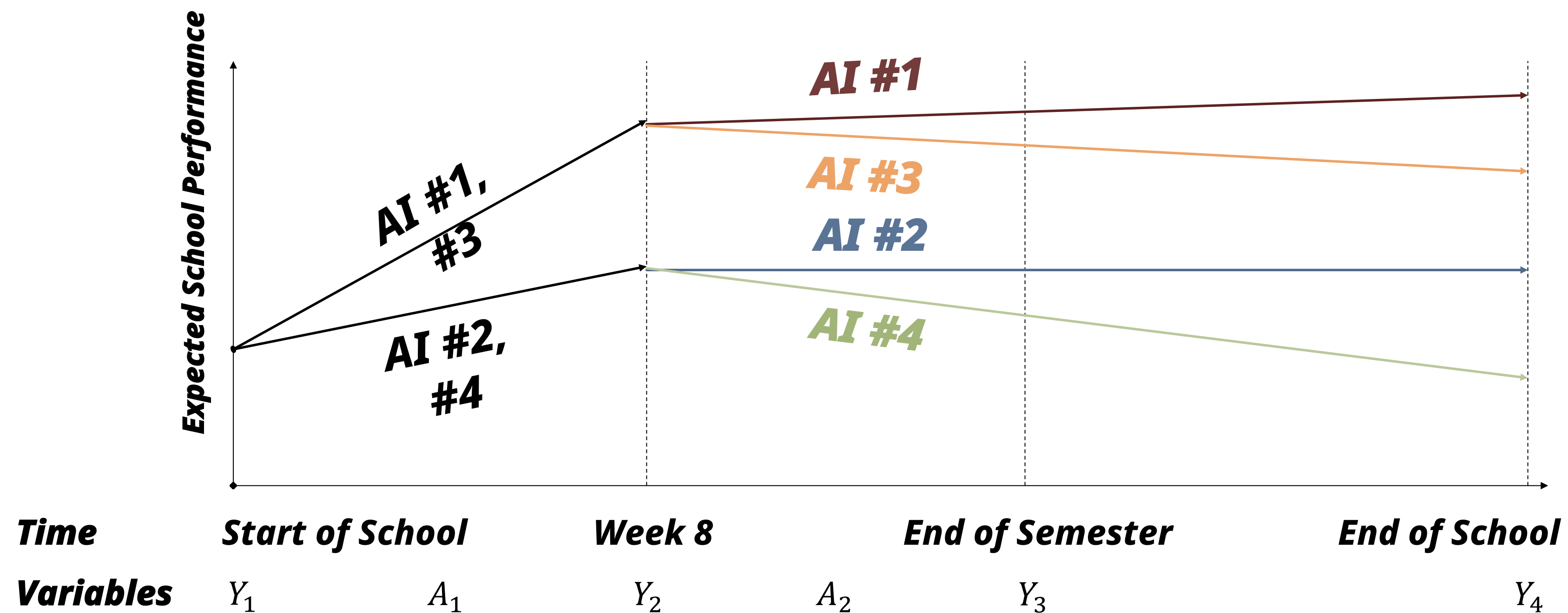
- The model we select should allow the outcome at each stage to be impacted only by intervention options that were offered prior to that stage.
- Failing to properly account for the ordering of the measurement occasions relative to the intervention options can lead to bias (see Lu et al., 2016).



Longitudinal Outcome Analysis

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

- Need to constrain the model parameters such that the temporal ordering is respected



Longitudinal Outcome Analysis

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

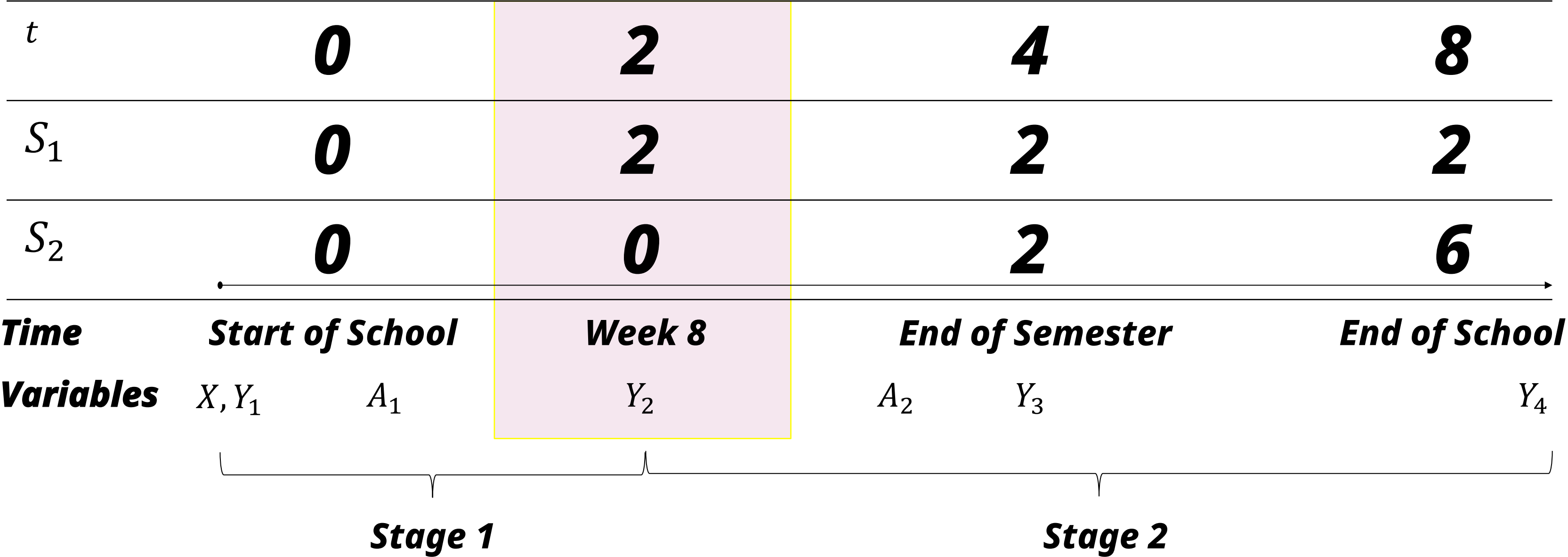
- We define two variables to help us construct an appropriately constrained model: S_1 and S_2



Longitudinal Outcome Analysis

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

- We define two variables to help us construct an appropriately constrained model: S_1 and S_2



Longitudinal Outcome Analysis

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

- We define two variables to help us construct an appropriately constrained model: S_1 and S_2

t	0	2	4	8		
S_1	0	2	2	2		
S_2	0	0	2	6		
Time	Start of School	Week 8	End of Semester	End of School		
Variables	X, Y_1	A_1	Y_2	A_2	Y_3	Y_4
	Stage 1			Stage 2		



Longitudinal Outcome Analysis

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

- We define two variables to help us construct an appropriately constrained model: S_1 and S_2

t	0	2	4	8		
S_1	0	2	2	2		
S_2	0	0	2	6		
Time	Start of School	Week 8	End of Semester	End of School		
Variables	X, Y_1	A_1	Y_2	A_2	Y_3	Y_4
	Stage 1			Stage 2		

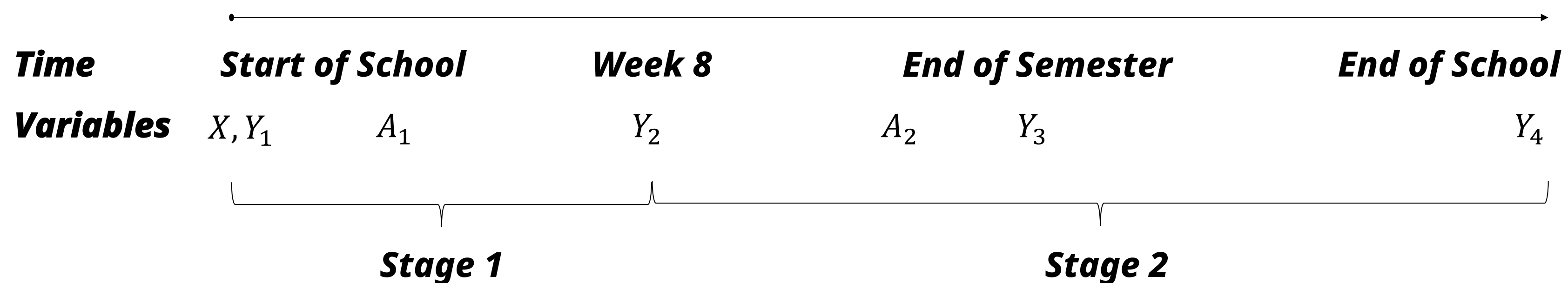


Longitudinal Outcome Analysis

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

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

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



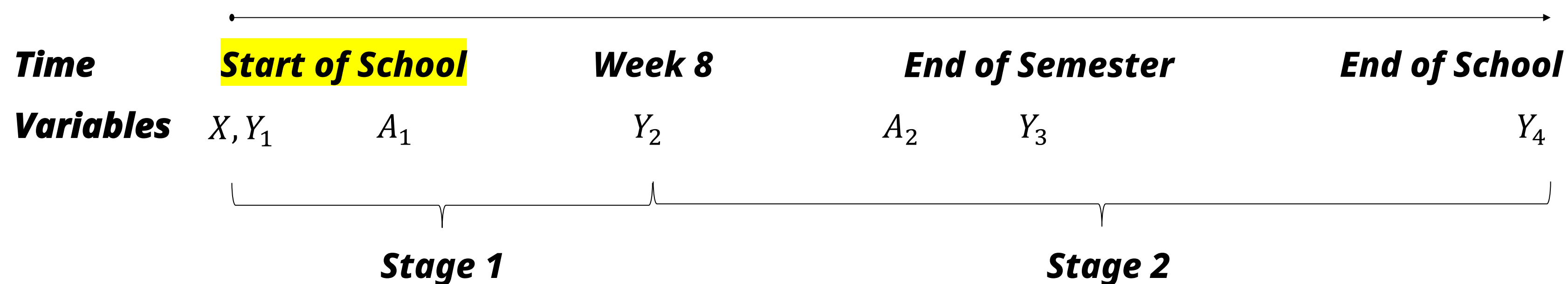
Longitudinal Outcome Analysis

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

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

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

β_0 : Expected school performance (SP) at beginning of school year



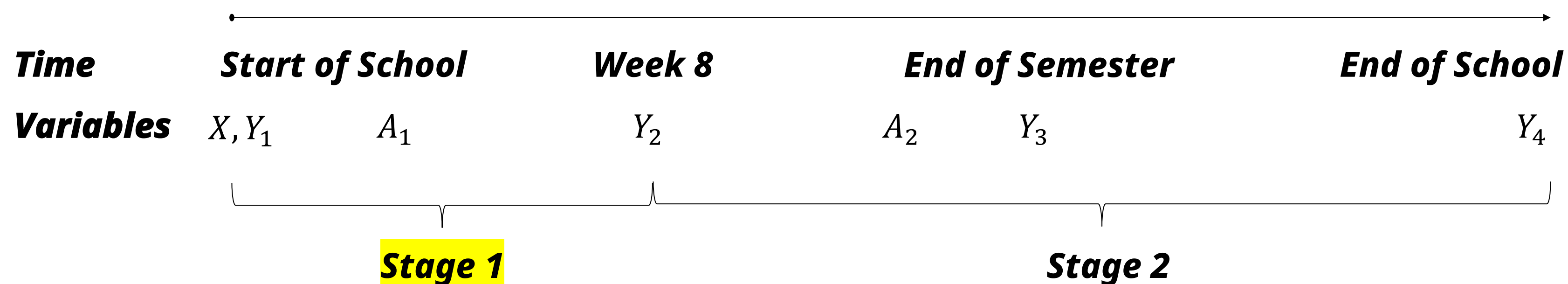
Longitudinal Outcome Analysis

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

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

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

β_1 : Stage 1 slope; expected monthly change in SP during stage 1



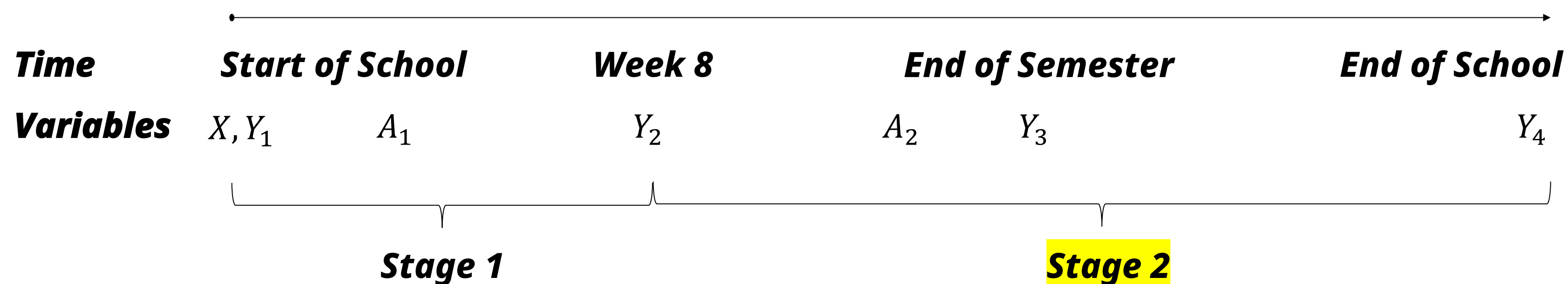
Longitudinal Outcome Analysis

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

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

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

β_2 : Stage 2 slope; Expected monthly change in SP during stage 2

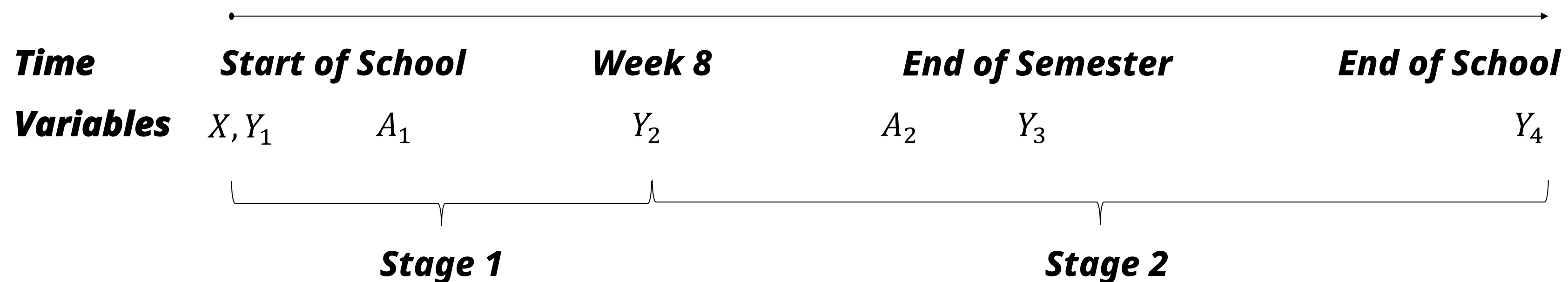


Longitudinal Outcome Analysis

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

- Now let's generalize our model to multiple adaptive interventions, taking care to respect the temporal ordering

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



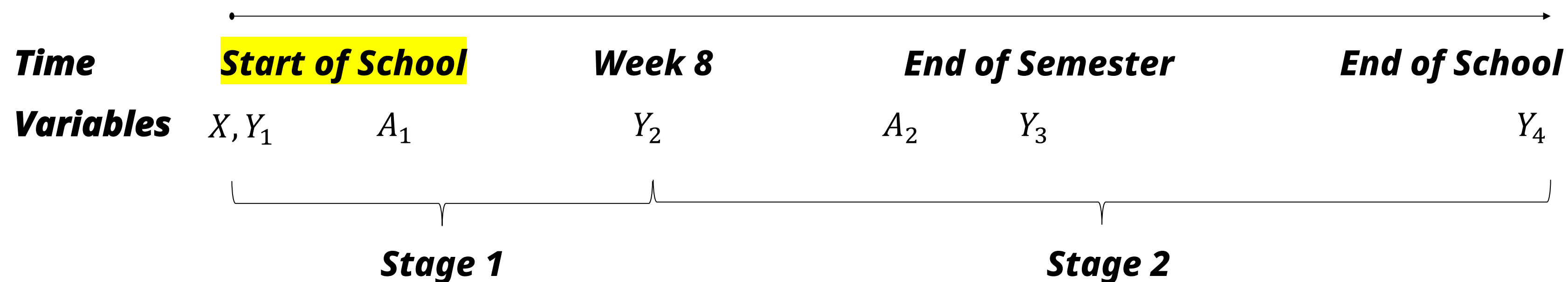
Longitudinal Outcome Analysis

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

- Now let's generalize our model to multiple adaptive interventions, taking care to respect the temporal ordering

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

β_0 : No change needed because the treatments cannot affect the mean SP at the start of the school year



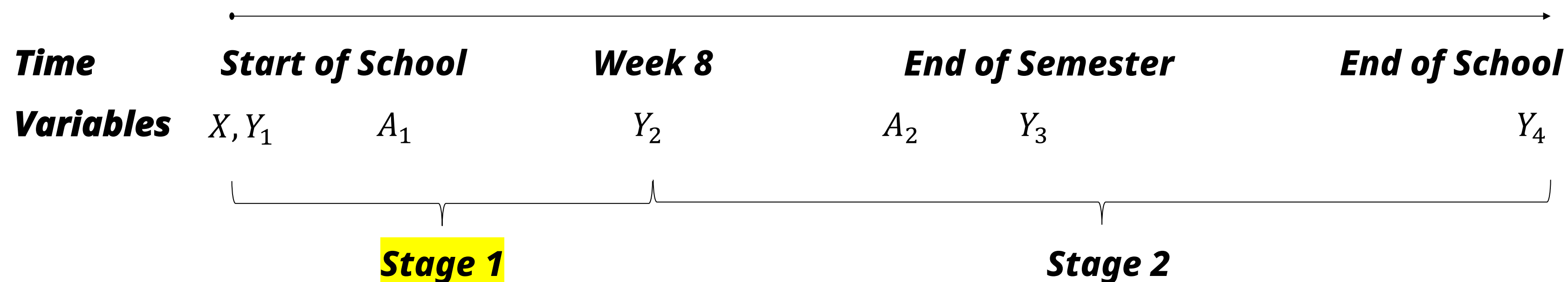
Longitudinal Outcome Analysis

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

- Now let's generalize our model to multiple adaptive interventions, taking care to respect the temporal ordering

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

β_1 : Replace with $(\beta_{10} + \beta_{11}A_1)$ because A_1 can affect the slope during stage 1



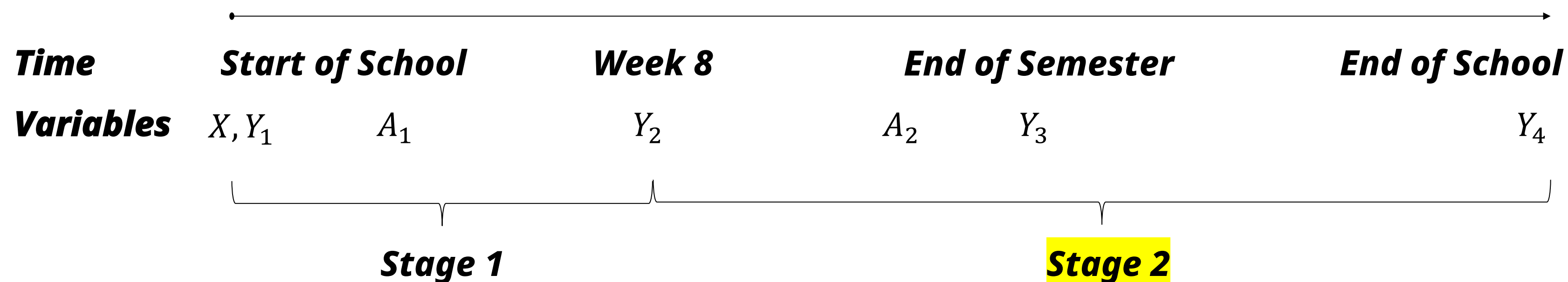
Longitudinal Outcome Analysis

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

- Now let's generalize our model to multiple adaptive interventions, taking care to respect the temporal ordering

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

β_2 : Replace with $(\beta_{20} + \beta_{21}A_1 + \beta_{22}A_2 + \beta_{23}A_1A_2)$ because A_1 and A_2 can affect the slope during stage 2

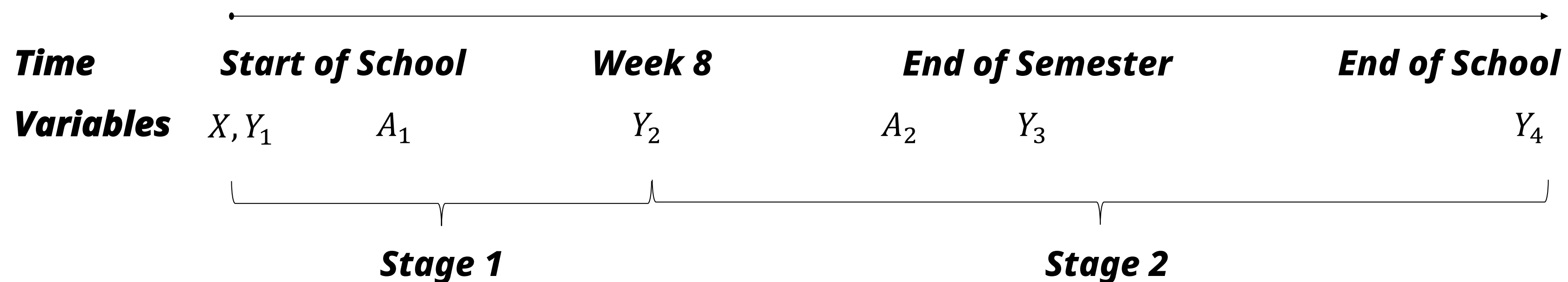


Longitudinal Outcome Analysis

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

- With these replacements, our final model becomes

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



Longitudinal Outcome Analysis

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

- The estimands are still linear combinations of parameters!



Longitudinal Outcome Analysis

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

A_1	A_2
1 BMOD	1 INTENSIF Y
-1 MED	-1 AUGMEN T

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

Mean of Y_4 under **AI #1 (MED, 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

A_1	A_2
1 BMOD	1 INTENSIFY
-1 MED	-1 AUGMENT

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

Mean of Y_4 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

A_1	A_2
1 BMOD	1 INTENSIFY
-1 MED	-1 AUGMENT

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

Difference in mean of Y_4 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

Overview of SMART designs with repeated outcome measures

Common scientific questions you can answer with repeated outcome measures

Data analysis methods for repeated outcome measures

Sample size considerations for planning SMARTs with repeated outcome measures



Longitudinal Outcome Sample Size for End-of-Study Comparisons

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

δ is the standardized effect size for the comparison

ρ 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

<i>Std. Effect Size</i>	<i>Within-Person Correlation</i>		
	$\rho = 0$	$\rho = 0.3$	$\rho = 0.6$
$\delta = 0.3$	559	508	358
$\delta = 0.5$	201	183	129



Additional Resources for Comparing Embedded AIs on a Longitudinal Outcome

R code for implementing the methodology

- See John Dziak's code here: <http://d3c.isr.umich.edu/code-library/>



References

- Lu, X., Nahum-Shani, I., Kasari, C., Lynch, K. G., Oslin, D. W., Pelham, W. E., ... & Almirall, D. (2016). Comparing dynamic treatment regimes using repeated-measures outcomes: modeling considerations in SMART studies. *Statistics in medicine*, 35(10), 1595-1615.
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