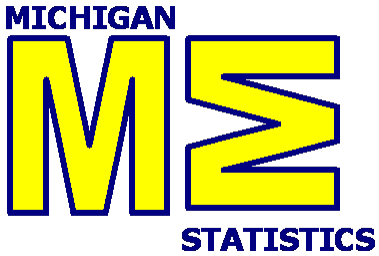
Getting SMART About Developing Individualized Sequences of Health Interventions

SBM, April 27

Susan A. Murphy & Daniel Almirall



Outline

- 3:20-3:45: Adaptive Treatment Strategies (Murphy)
- 4:00-4:25: SMART Experimental Design (Murphy)
- 4:40-5:05: Interesting Primary Analyses (Almirall)
- 5:20-5:45: Interesting Secondary Analyses (Almirall)
- *Question Slips and Exercises at end of each module*

Adaptive Treatment Strategies

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Institute for Social Research
Survey Research Center
SRC

The Methodology Center

MICHIGAN
STATISTICS

Outline

- What are Adaptive Treatment Strategies?
- Why use Adaptive Treatment Strategies?
- Adaptive Treatment Strategy Design Goals
- What does an Adaptive Treatment Strategy include?
- Summary & Discussion

Adaptive Treatment Strategies

• Are individually tailored time-varying treatments composed of

- a sequence of critical treatment decisions
- tailoring variables
- decision rules, one per critical decision; decision rules input tailoring variables and output an individualized treatment recommendation.

•Operationalize clinical practice.

Adaptive Aftercare for Alcohol Dependent Individuals

- Critical treatment decisions: which treatment to provide first?; which treatment to provide second?
- Tailoring variable: heavy drinking days

Decision Rules

First alcohol dependent individuals are provided Naltrexone along with Medical Management.

Second if an individual experiences 3 or more heavy drinking days prior to 8 weeks on Naltrexone then the individual's Naltrexone treatment is augmented with Combine Behavioral Intervention.

Or if the individual successfully completes 8 weeks with fewer than 3 heavy drinking days then the individual is provided a prescription to Naltrexone along with Telephone Disease Management.

Adaptive Treatment Strategies

• From the individual/patient/client's point of view: a sequence of (individualized) treatments

• From the clinical scientist's point of view: a sequence of decision rules that recommend one or more treatments at each critical decision.

More examples of critical treatment decisions and tailoring variables

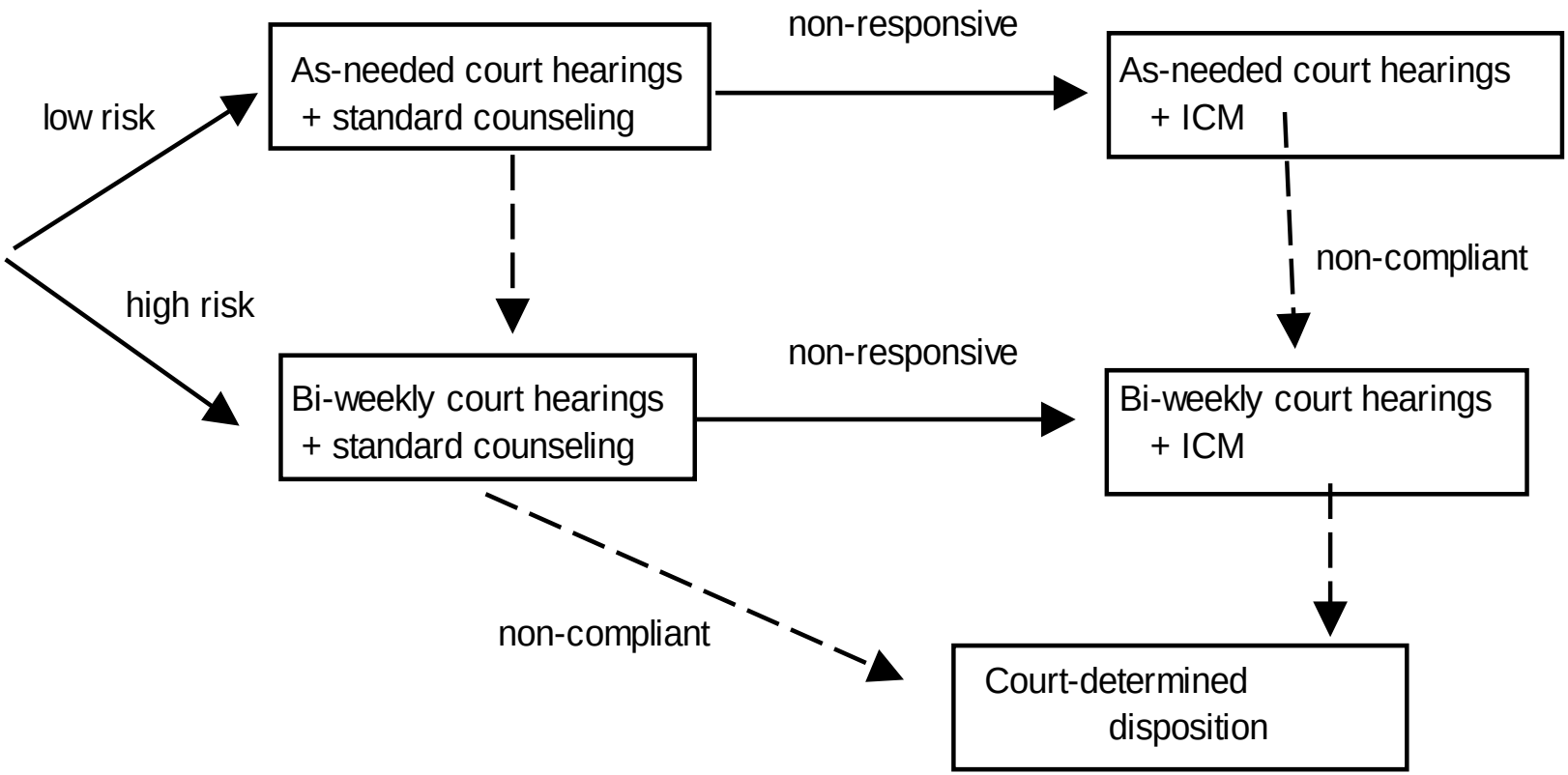
• Critical treatment decisions: how long to try the first treatment?; how should a treatment be delivered?; how intensive should a treatment be? When to stop/start treatment?

• Tailoring variables: severity of illness, presence of comorbid mental or physical conditions, family support, adherence to present treatment, side effects resulting from present treatment, symptoms while in treatment.

Another Example of an Adaptive Treatment Strategy

- Adaptive Drug Court Program for drug abusing offenders.
- Goal is to minimize recidivism and drug use.
- Marlowe et al. (2008)

Adaptive Drug Court Program



Other Examples of Adaptive Treatment Strategies

- Brooner et al. (2002, 2007) Treatment of Opioid Addiction
- McKay (2009) Treatment of Substance Use Disorders
- Marlowe et al. (2008) Drug Court
- Rush et al. (2003) Treatment of Depression

Why Adaptive Treatment Strategies?

- High heterogeneity in need for or response to any one treatment
  - What works for one person may not work for another
- Improvement often marred by relapse
- Lack of adherence or excessive burden is common
- Intervals during which more intense treatment is required alternate with intervals in which less treatment is sufficient

Why not combine all possible efficacious therapies and provide all of these to patient now and in the future?

- Treatment incurs side effects and substantial burden, particularly over longer time periods.
- Problems with adherence:
  - Variations of treatment or different delivery mechanisms may increase adherence
  - Excessive treatment may lead to non-adherence
- Treatment is costly (Would like to devote additional resources to patients with more severe problems)

More is not always better!

Treatment Design Goals

- Maximize the strength of the adaptive treatment strategy
  - by well chosen tailoring variables, well measured tailoring variables, & well conceived decision rules

Treatment Design Goals

- Maximize replicability in future experimental and real-world implementation conditions
  - by fidelity of implementation & by clearly defining the treatment strategy

Parts of the Adaptive Treatment Strategy

- Choice of the Tailoring Variable
- Measurement of the Tailoring Variable
- Decision Rules linking Tailoring Variables to Treatment Decisions
- Implementation of the Decision Rules

Choice of Tailoring Variable

- Significant differences in effect sizes in a comparison of fixed treatments as a function of characteristics.

- Tailoring variable: individual, family, contextual characteristics; individual, family outcomes to treatment

Adaptive Drug Court Program

- Offenders who return to drug use while receiving counseling need additional help to maintain a drug-free lifestyle.
- Tailoring variable is positive urine test
- Providing ICM to offenders who are able to stay drug free is costly.

Technical Interlude!

s=tailoring variable

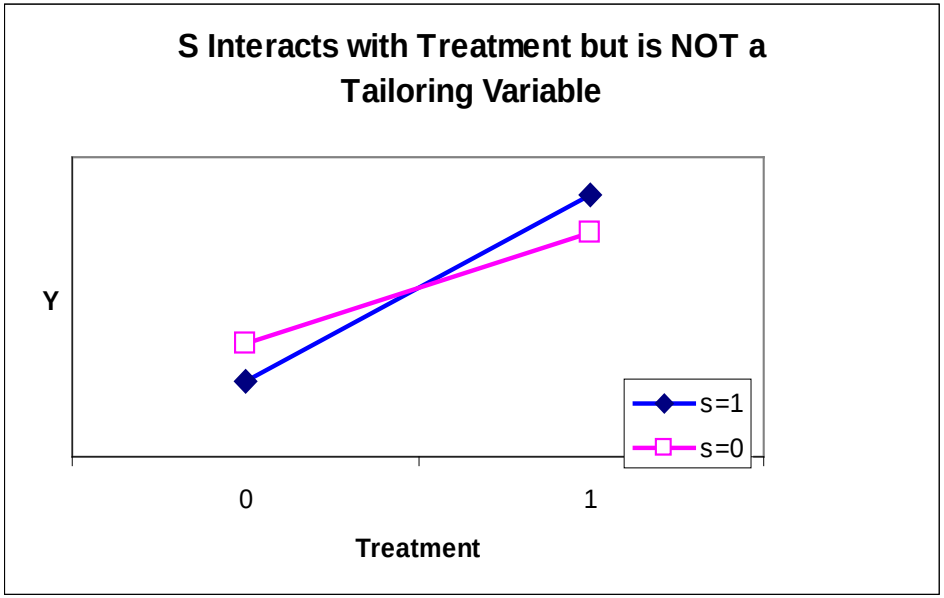
t=treatment type (0 or 1)

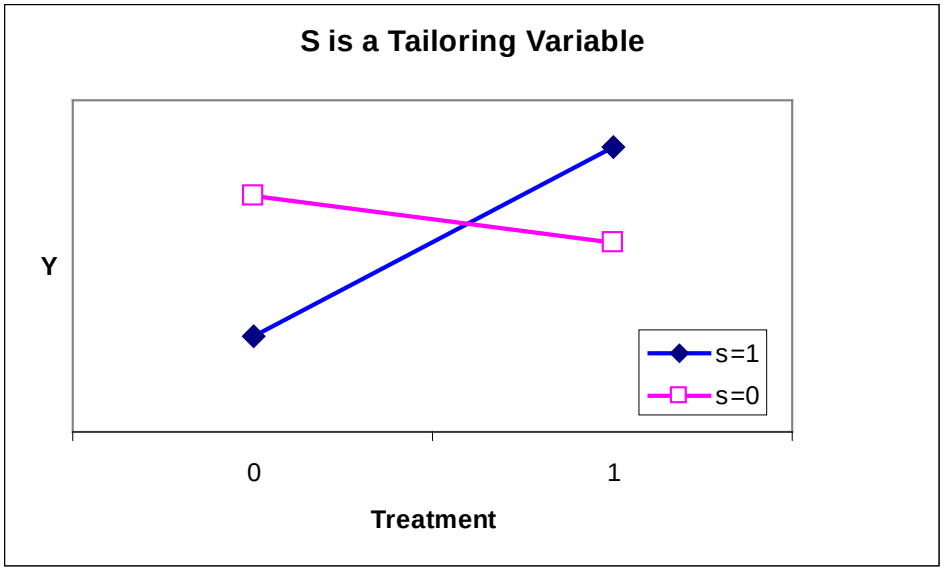
Y=primary outcome (high is preferred)

$$Y=\beta_0 + \beta_1 s + \beta_2 t + \beta_3 st + error$$

$$= \beta_0 + \beta_1 s + (\beta_2 + \beta_3 s)t + error$$

If $(\beta_2 + \beta_3 s)$ is zero or negative for some *s* and positive for others then *s* is a tailoring variable.


S Interacts with Treatment but is NOT a Tailoring Variable
Y
s=1
s=0
0
1
Treatment


S is a Tailoring Variable
Y
s=1
s=0
0
1
Treatment

Measurement of Tailoring Variables

- Reliability -- high signal to noise ratio
- Validity -- unbiased

Derivation of Decision Rules

- Articulate a theoretical model for how treatment effect on key outcomes should differ across values of the moderator.
- Use scientific theory and prior clinical experience.
- Use prior experimental and observational studies.
- Discuss with research team and clinical staff, “What dosage would be best for people with this value on the tailoring variable?”

Derivation of Decision Rules

- Good decision rules are objective, are operationalized.
- Strive for comprehensive rules (this is hard!) – cover situations that can occur in practice, including when the tailoring variable is missing or unavailable.

Implementation

- Try to implement rules universally, applying decision rules consistently across subjects, time, site & staff members.

- Document values of tailoring variable!

Implementation

- Exceptions to the rules should be made only after group discussions and with group agreement.
- If it is necessary to make an exception, document this so you can describe the implemented treatment.

Summary & Discussion

•Research is needed to build a theoretical literature that can provide guidance:

- in identifying tailoring variables,
- in the development of reliable and valid indices of the tailoring variables that can be used in the course of repeated clinical assessments

Summary & Discussion

•Research is needed on how we might use existing experimental and observational studies to

- Identify useful tailoring variables
- Formulate best rules.

•Next up!: Experimental Study designs for use in finding good tailoring variables and rules.

Question, Answer, & Practice Exercise

Practice Exercise:

Write down 3-4 simple adaptive treatment strategies to address a chronic disorder in your field.

Sequential, Multiple Assignment, Randomized Trials

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Outline

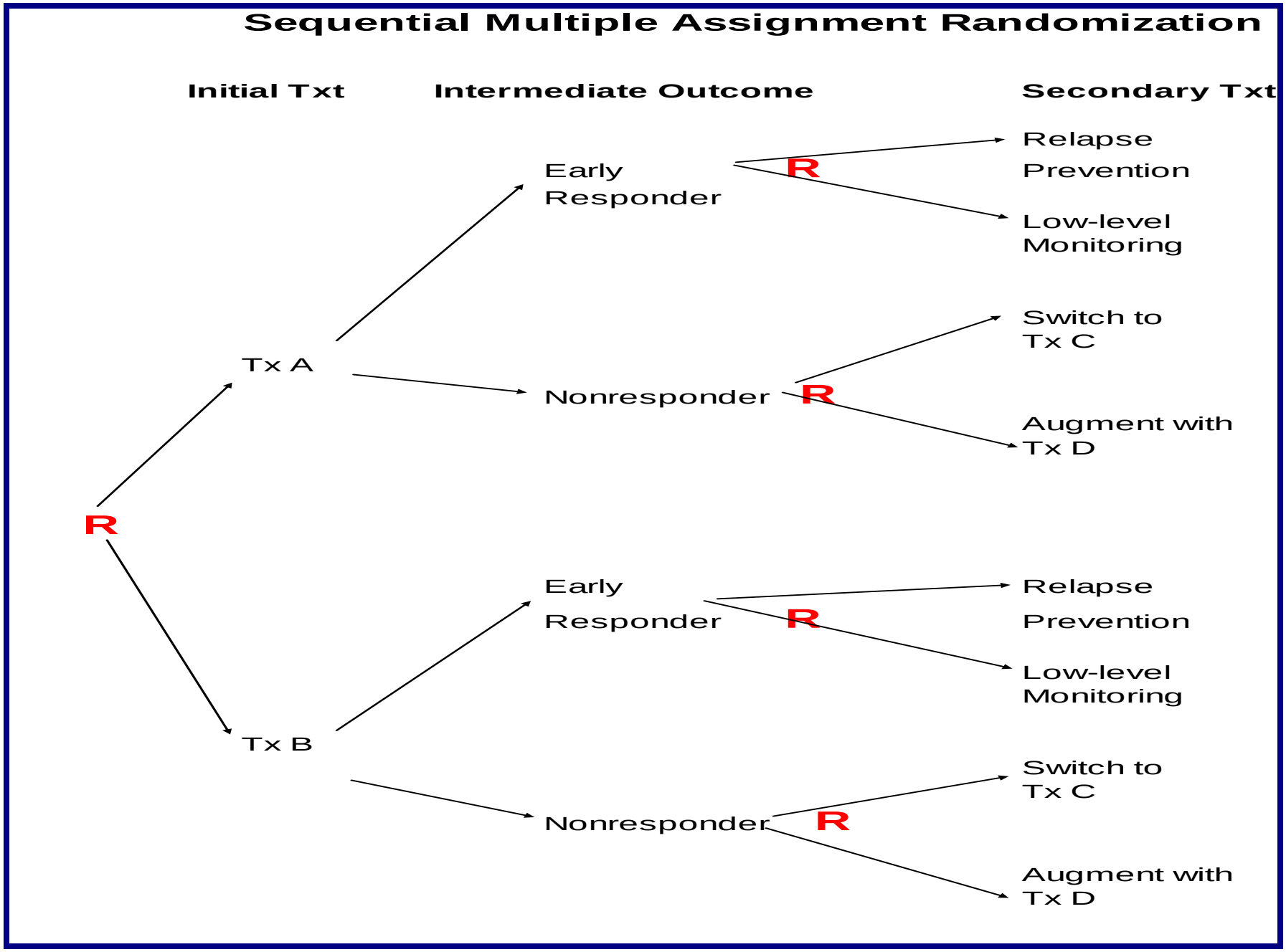
- What are Sequential Multiple Assignment Trials (SMARTs)?
- Why SMART experimental designs?
  - "new" clinical trial design
- Trial Design Principles and Analysis
- Examples of SMART Studies
- Summary & Discussion

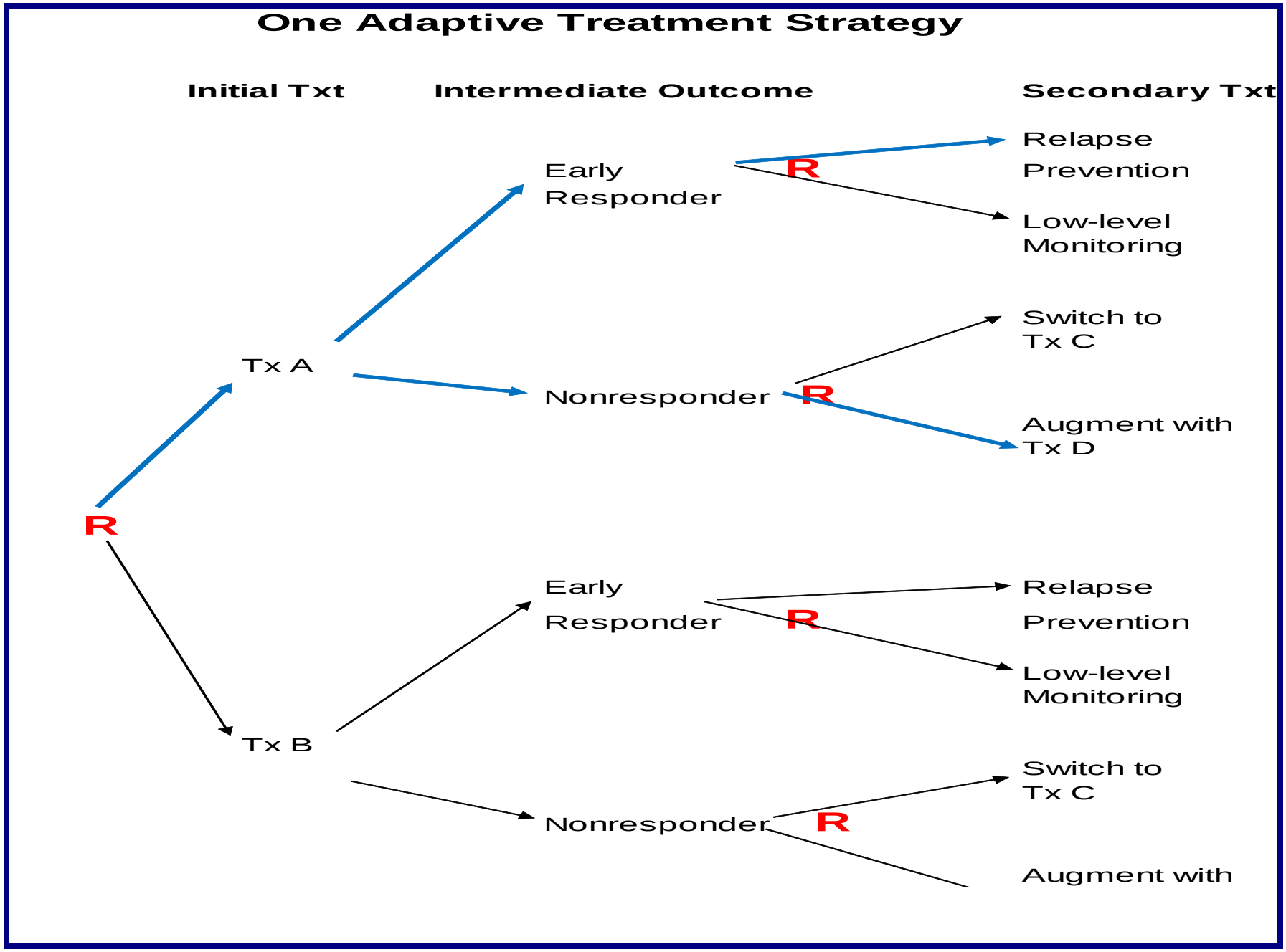
Why SMART Trials?

What is a sequential multiple assignment randomized trial (SMART)?

These are multi-stage trials; each stage corresponds to a critical decision and a randomization takes place at each critical decision.

Goal is to inform the construction of adaptive treatment strategies.


Sequential Multiple Assignment Randomization
Initial Txt
Intermediate Outcome
Secondary Txt
R
Tx A
Tx B
Early Responder
Nonresponder
Early Responder
Nonresponder
R
R
R
R
Relapse Prevention
Low-level Monitoring
Switch to Tx C
Augment with Tx D
Relapse Prevention
Low-level Monitoring
Switch to Tx C
Augment with Tx D


One Adaptive Treatment Strategy
Initial Txt
Intermediate Outcome
Secondary Txt
R
Tx A
Tx B
Early Responder
Nonresponder
Early Responder
Nonresponder
R
R
R
R
Relapse Prevention
Low-level Monitoring
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Augment with Tx D
Relapse Prevention
Low-level Monitoring
Switch to Tx C
Augment with

Alternate Approach to Constructing an Adaptive Treatment Strategy

- Why not use data from multiple trials to construct the adaptive treatment strategy?
- Choose the best initial treatment on the basis of a randomized trial of initial treatments and choose the best secondary treatment on the basis of a randomized trial of secondary treatments.

Delayed Therapeutic Effects

Why not use data from multiple trials to construct the adaptive treatment strategy?

Positive synergies: Treatment A may not appear best initially but may have enhanced long term effectiveness when followed by a particular maintenance treatment. Treatment A may lay the foundation for an enhanced effect of particular subsequent treatments.

Delayed Therapeutic Effects

Why not use data from multiple trials to construct the adaptive treatment strategy?

Negative synergies: Treatment A may produce a higher proportion of responders but also result in side effects that reduce the variety of subsequent treatments for those that do not respond. Or the burden imposed by treatment A may be sufficiently high so that nonresponders are less likely to adhere to subsequent treatments.

Prescriptive Effects

Why not use data from multiple trials to construct the adaptive treatment strategy?

Treatment A may not produce as high a proportion of responders as treatment B but treatment A may elicit symptoms that allow you to better match the subsequent treatment to the patient and thus achieve improved response to the sequence of treatments as compared to initial treatment B.

Sample Selection Effects

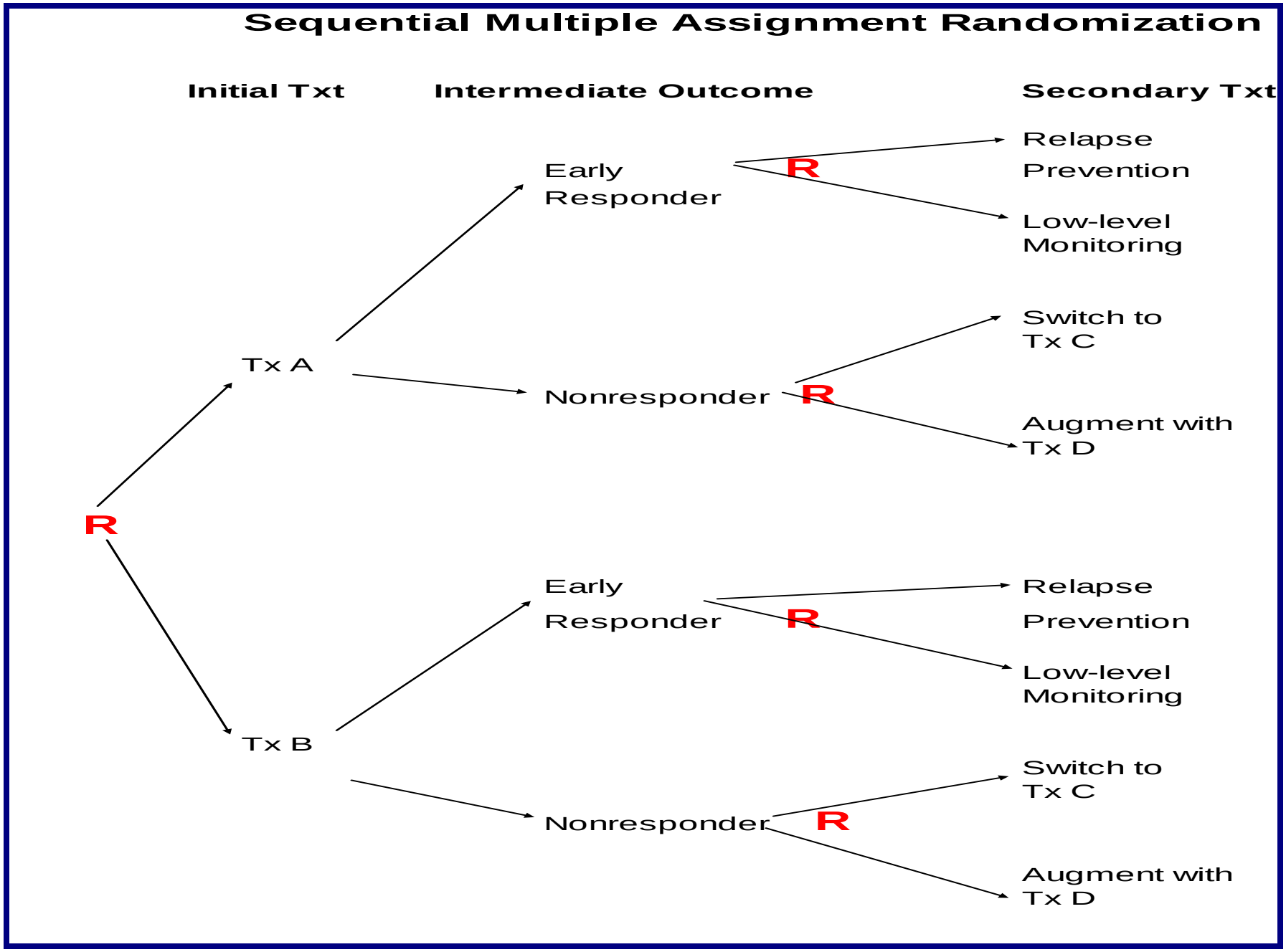
Why not use data from multiple trials to construct the adaptive treatment strategy?

Subjects who ***will enroll in***, who ***remain in or*** who ***are adherent in*** the trial of the initial treatments may be quite different from the subjects in SMART.

Summary:

- When evaluating and comparing initial treatments, *in a sequence of treatments*, we need to take into account, e.g. control, the effects of the secondary treatments thus SMART

- Standard one-stage randomized trials may yield information about different populations from SMART trials.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Examples of "SMART" designs:

- CATIE (2001) Treatment of Psychosis in Schizophrenia
- Pelham (primary analysis) Treatment of ADHD
- Oslin (primary analysis) Treatment of Alcohol Dependence
- Jones (in field) Treatment for Pregnant Women who are Drug Dependent
- Kasari (in field) Treatment of Children with Autism
- McKay (in field) Treatment of Alcohol and Cocaine Dependence

SMART Design Principles

•KEEP IT SIMPLE: At each stage (critical decision point), restrict class of treatments only by ethical, feasibility or strong scientific considerations. Use a low dimension summary (responder status) instead of all intermediate outcomes (adherence, etc.) to restrict class of next treatments.

•Collect intermediate outcomes that might be useful in ascertaining for whom each treatment works best; information that might enter into the adaptive treatment strategy.

SMART Design Principles

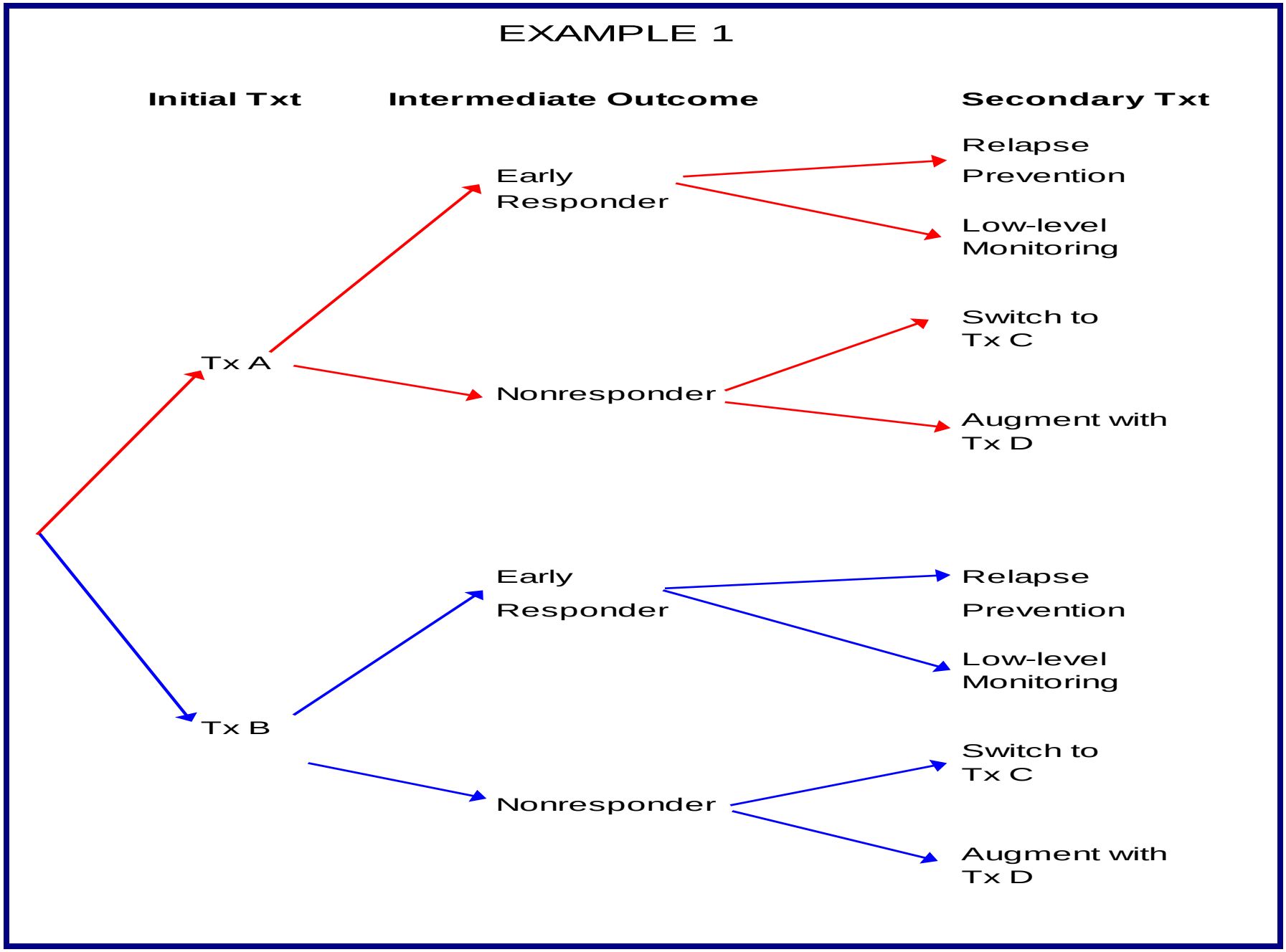
- Choose primary hypotheses that are both scientifically important and aids in developing the adaptive treatment strategy.
    - Power trial to address these hypotheses.

- Choose secondary hypotheses that further develop the adaptive treatment strategy and use the randomization to eliminate confounding.
    - Trial is not necessarily powered to address these hypotheses.

SMART Designing Principles: Primary Hypothesis

- EXAMPLE 1: (*sample size is highly constrained*): Hypothesize that controlling for the secondary treatments, the initial treatment A results in lower symptoms than the initial treatment B.

- EXAMPLE 2: (*sample size is less constrained*): Hypothesize that among non-responders a switch to treatment C results in lower symptoms than an augment with treatment D.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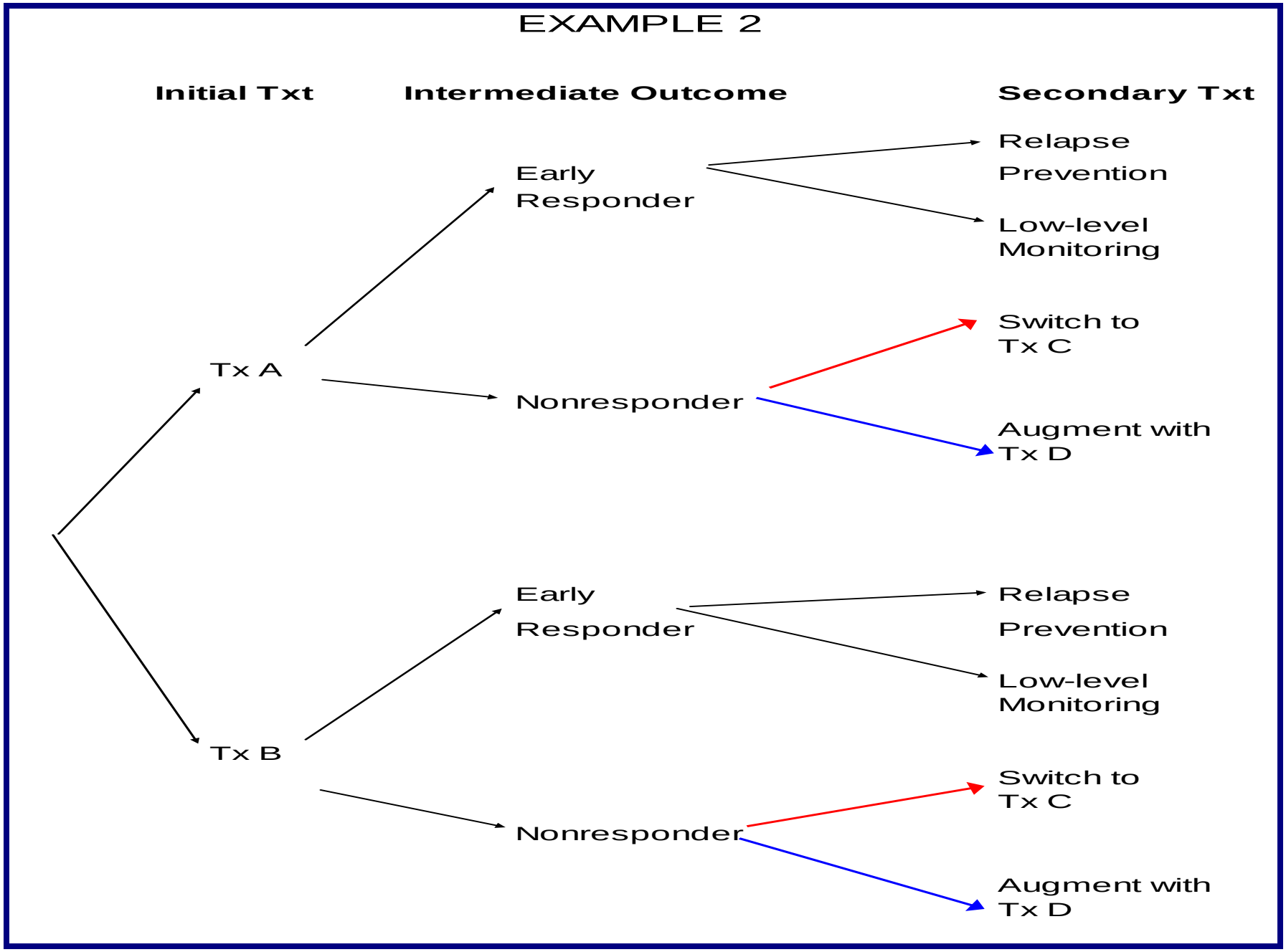

EXAMPLE 2
Initial Txt
Intermediate Outcome
Secondary Txt
Tx A
Early Responder
Relapse Prevention
Low-level Monitoring
Nonresponder
Switch to Tx C
Augment with Tx D
Tx B
Early Responder
Relapse Prevention
Low-level Monitoring
Nonresponder
Switch to Tx C
Augment with Tx D

SMART Designing Principles: Sample Size Formula

- EXAMPLE 1: (sample size is highly constrained): Hypothesize that given the secondary treatments provided, the initial treatment A results in lower symptoms than the initial treatment B. *Sample size formula is same as for a two group comparison.*
- EXAMPLE 2: (sample size is less constrained): Hypothesize that among non-responders a switch to treatment C results in lower symptoms than an augment with treatment D. *Sample size formula is same as a two group comparison of non-responders.*

Sample Sizes

N=trial size

	Example 1	Example 2
$\Delta\mu/\sigma$ =.3	N = 402	N = 402/initial nonresponse rate
$\Delta\mu/\sigma$ =.5	N = 146	N = 146/initial nonresponse rate

α = .05, power =1 – β=.85

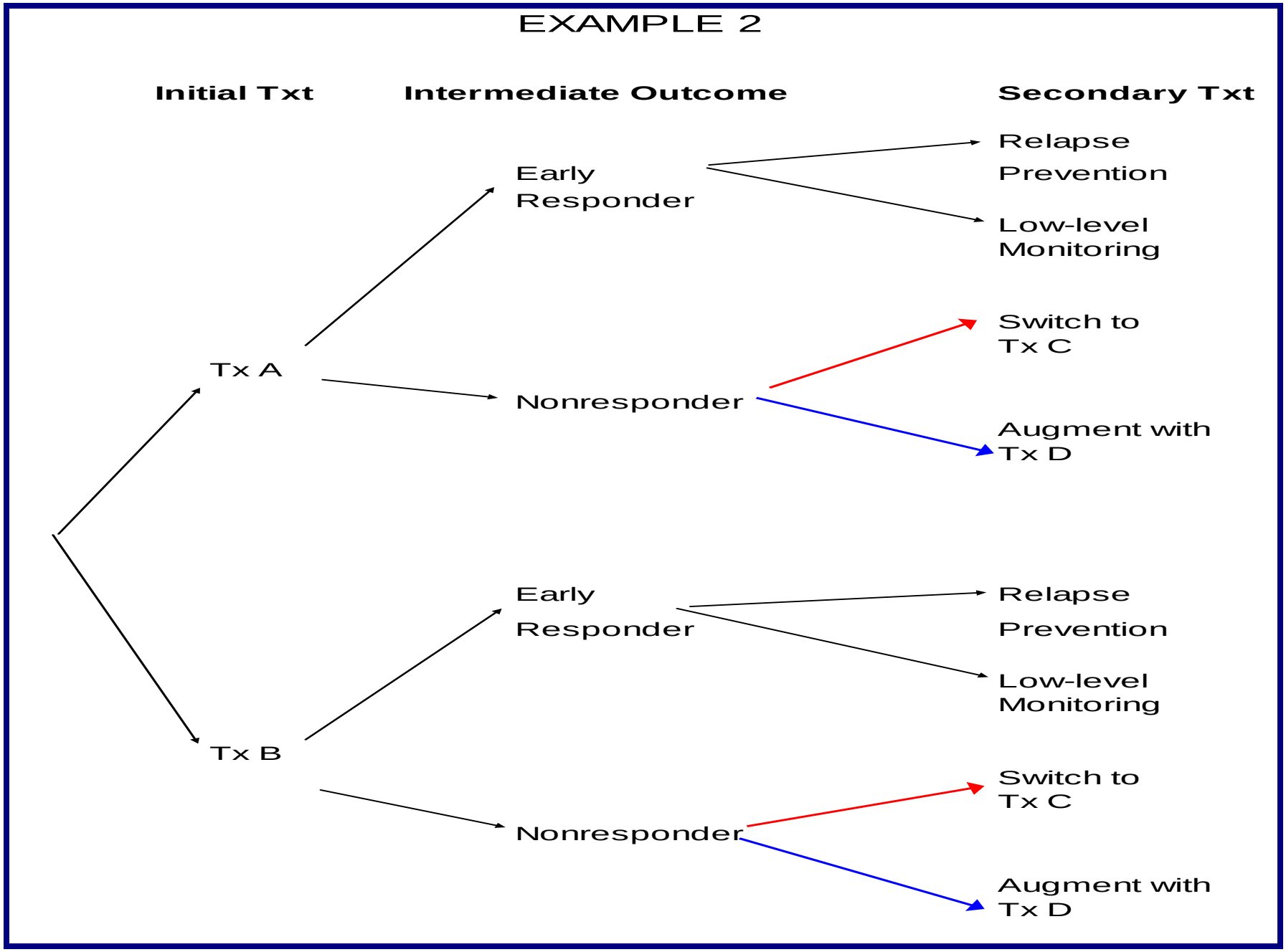
An analysis that is less useful in the development of adaptive treatment strategies:

Decide whether treatment A is better than treatment B by comparing intermediate outcomes (proportion of early responders).

SMART Designing Principles

•Choose secondary hypotheses that further develop the adaptive treatment strategy and use the randomization to eliminate confounding.

•EXAMPLE: Hypothesize that *non-adhering* non-responders will exhibit lower symptoms if their treatment is augmented with D as compared to an switch to treatment C (e.g. augment D includes motivational interviewing).


EXAMPLE 2
Initial Txt
Intermediate Outcome
Secondary Txt
Tx A
Early Responder
Relapse Prevention
Low-level Monitoring
Nonresponder
Switch to Tx C
Augment with Tx D
Tx B
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Outline

- What are Sequential Multiple Assignment Trials (SMARTs)?
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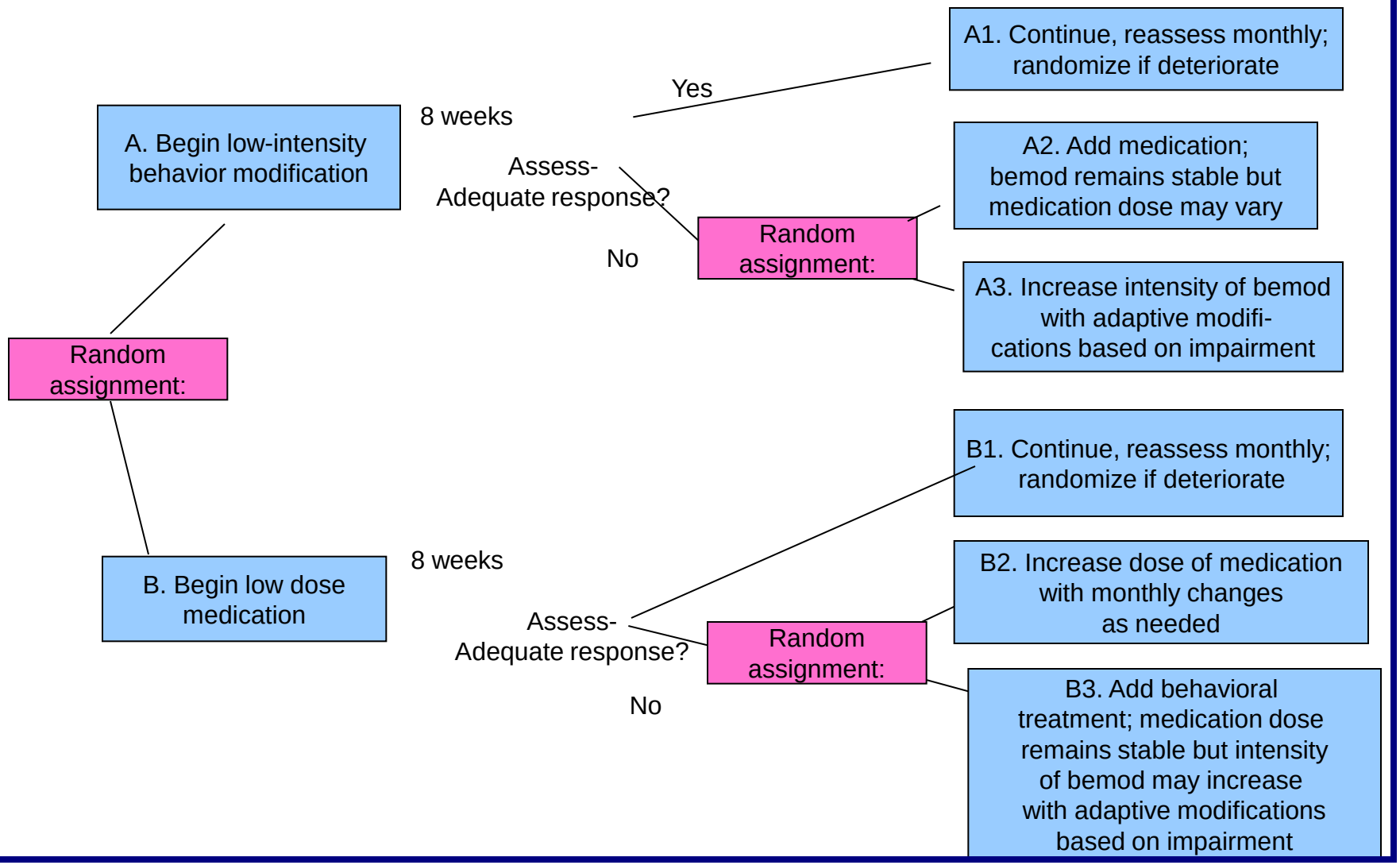
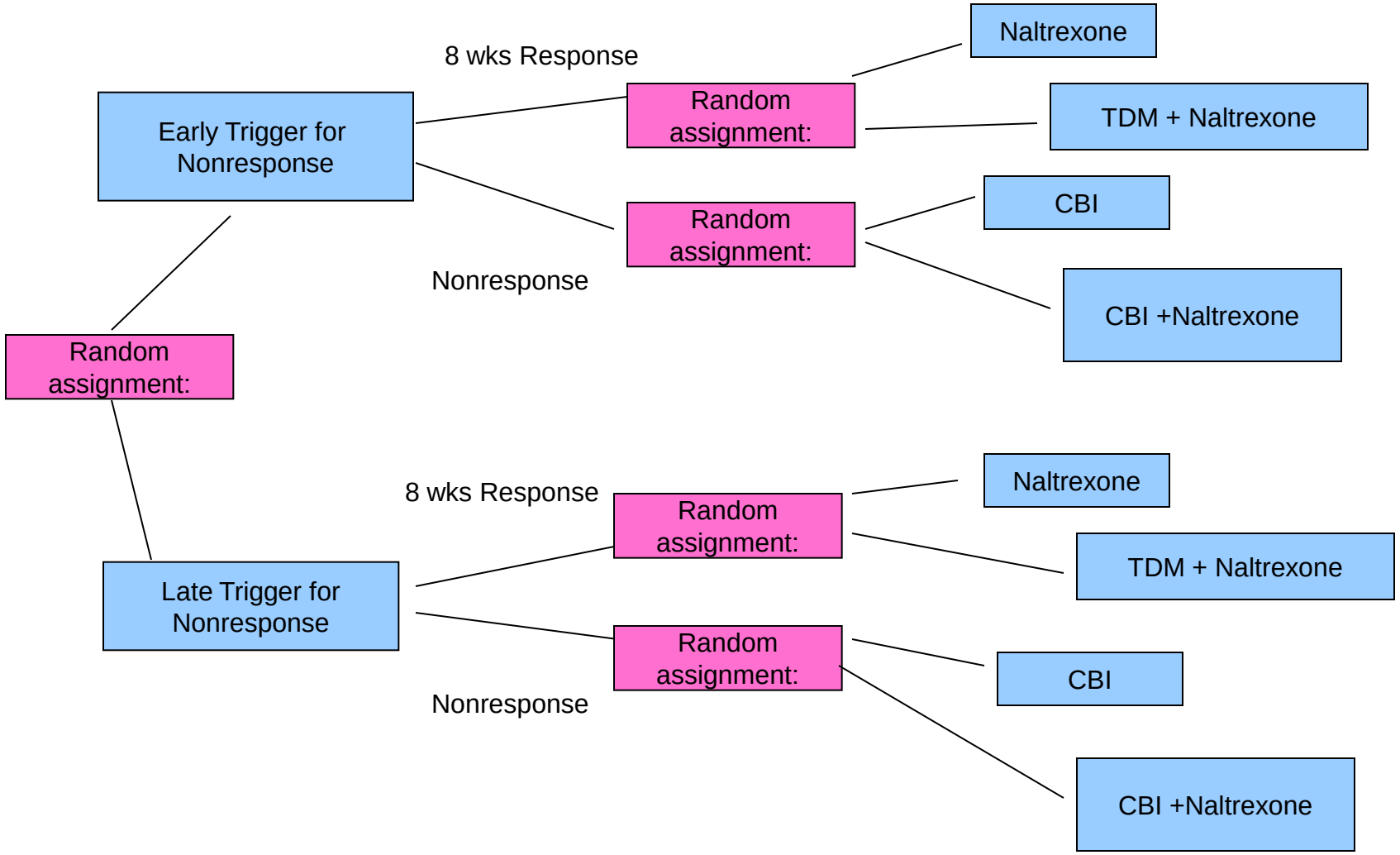
Pelham ADHD Study



Oslin ExTENd



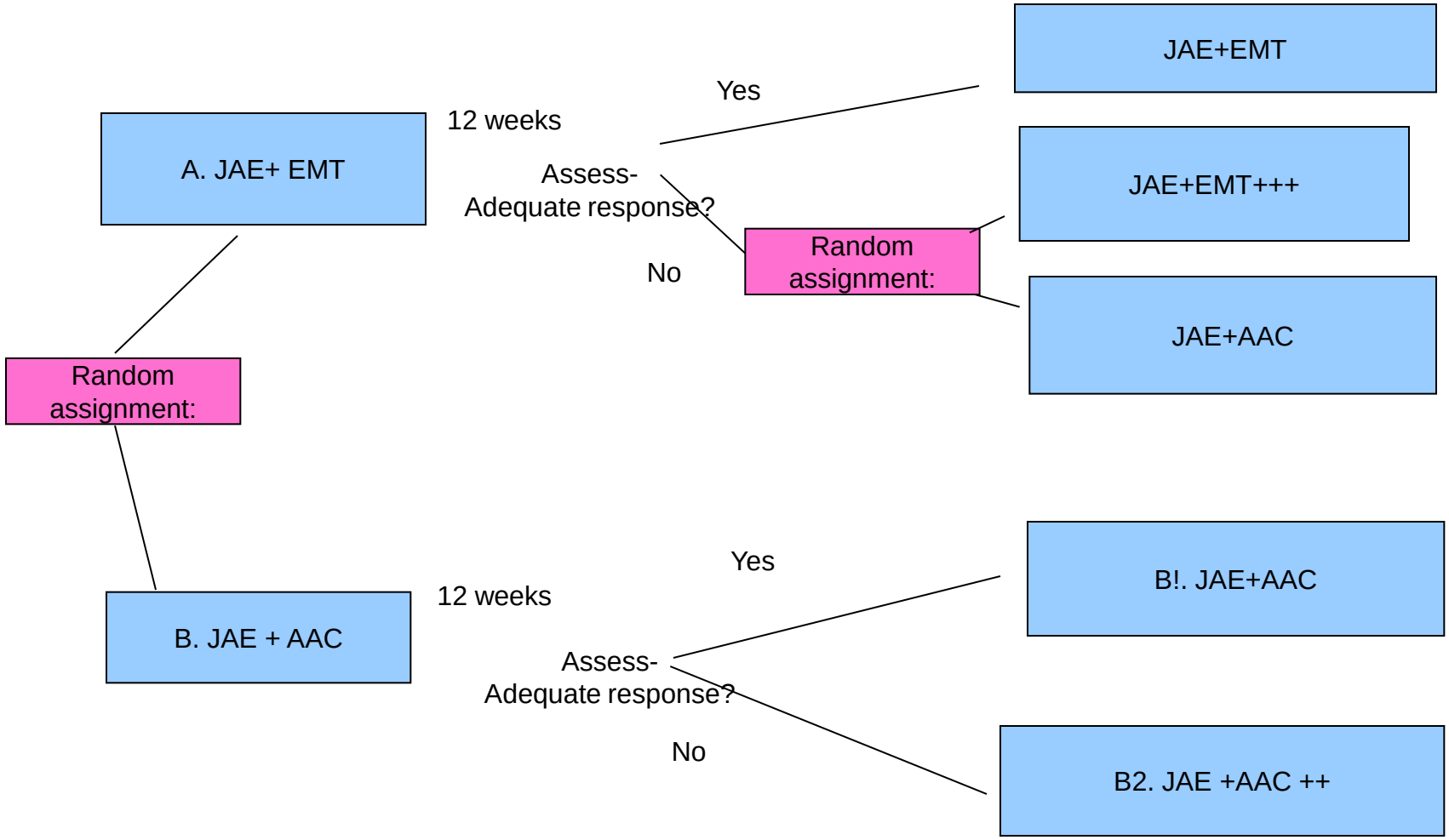
Discussion

- We have a sample size formula that specifies the sample size necessary to detect an adaptive treatment strategy that results in a mean outcome δ standard deviations better than the other strategies with 90% probability (A. Oetting, J. Levy & R. Weiss are collaborators)

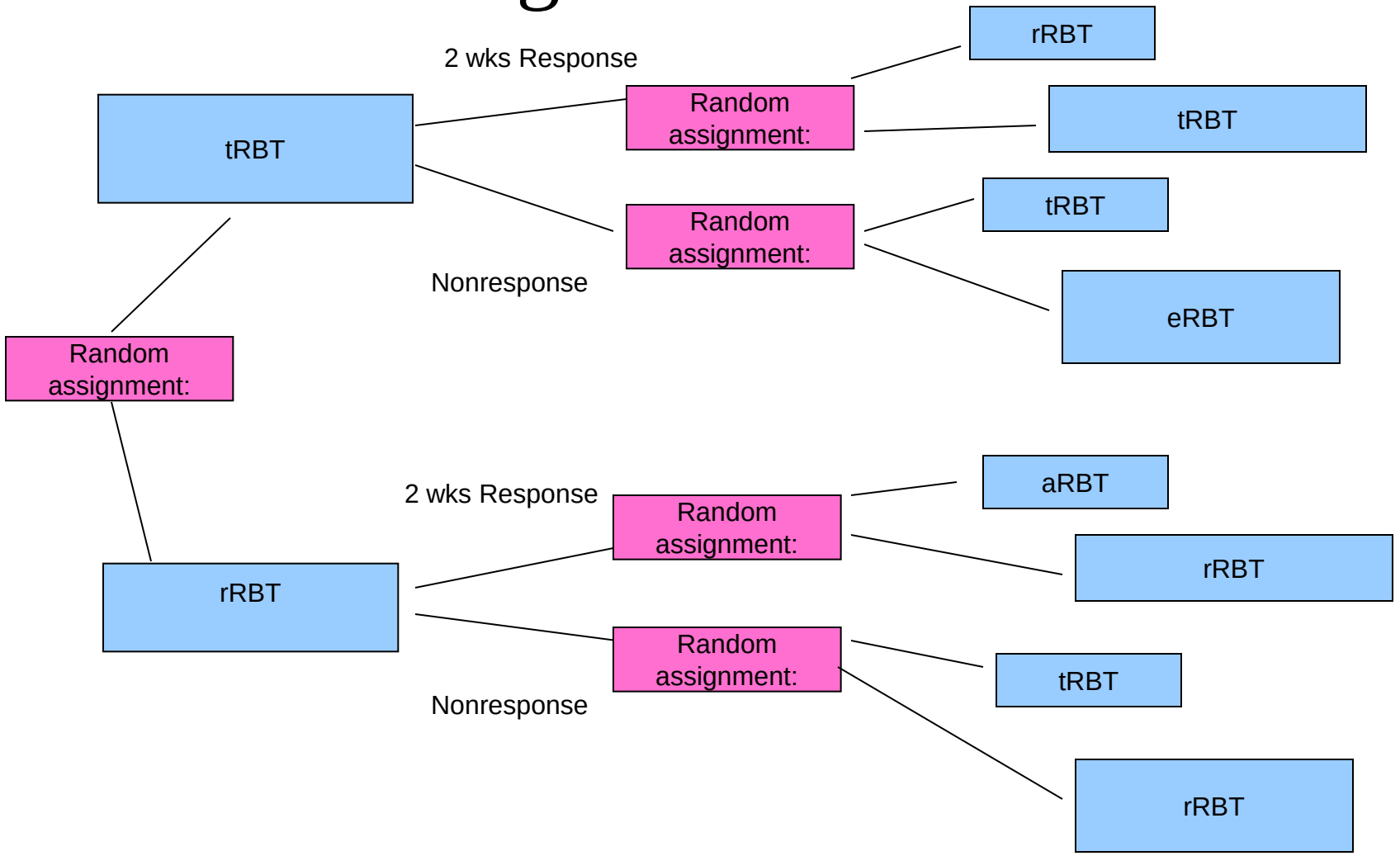
- We also have sample size formula that specify the sample size for time-to-event studies.

- Aside: Non-adherence is an outcome (like side effects) that indicates need to tailor treatment.

Kasari Autism Study



Jones' Study for Drug-Addicted Pregnant Women



Question, Answer, & Practice Exercise

Practice Exercise:

Using the 3-4 adaptive treatment strategies you came up with in Module 1, can you think of a simple SMART design that would be useful to you?

Primary Aims Using Data Arising from a SMART

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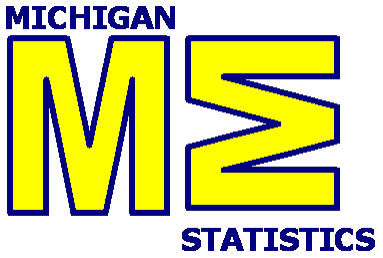
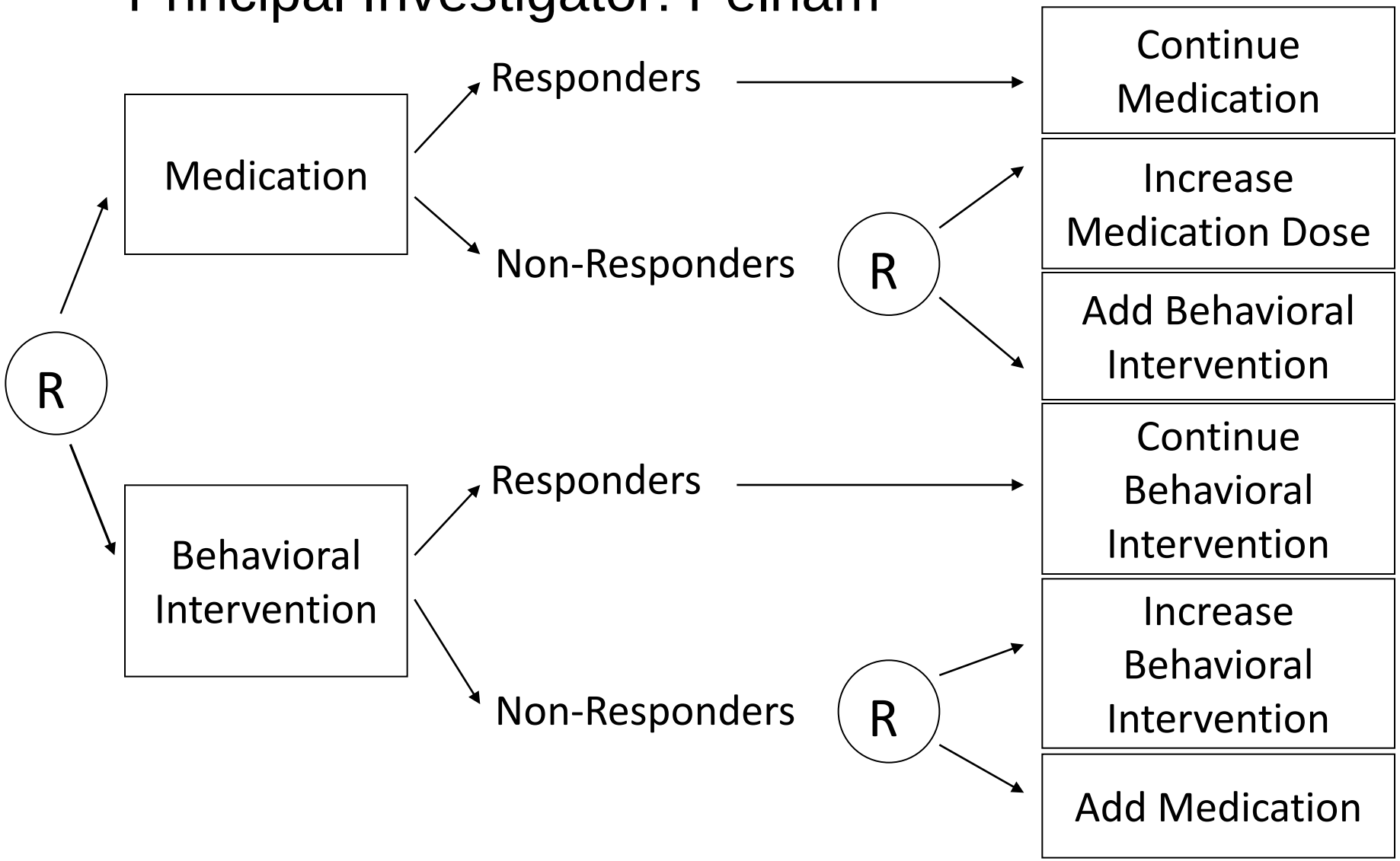


Primary Aims Outline

- Review the *Adaptive Interventions for Children with ADHD Study* design
  - This is a SMART design
- Two typical primary research questions in a SMART
  - Q1: Main effect of first-line treatment?
  - Q2: Comparison of two embedded ATS?
- Results from a worked example
- SAS code snippets for the worked example

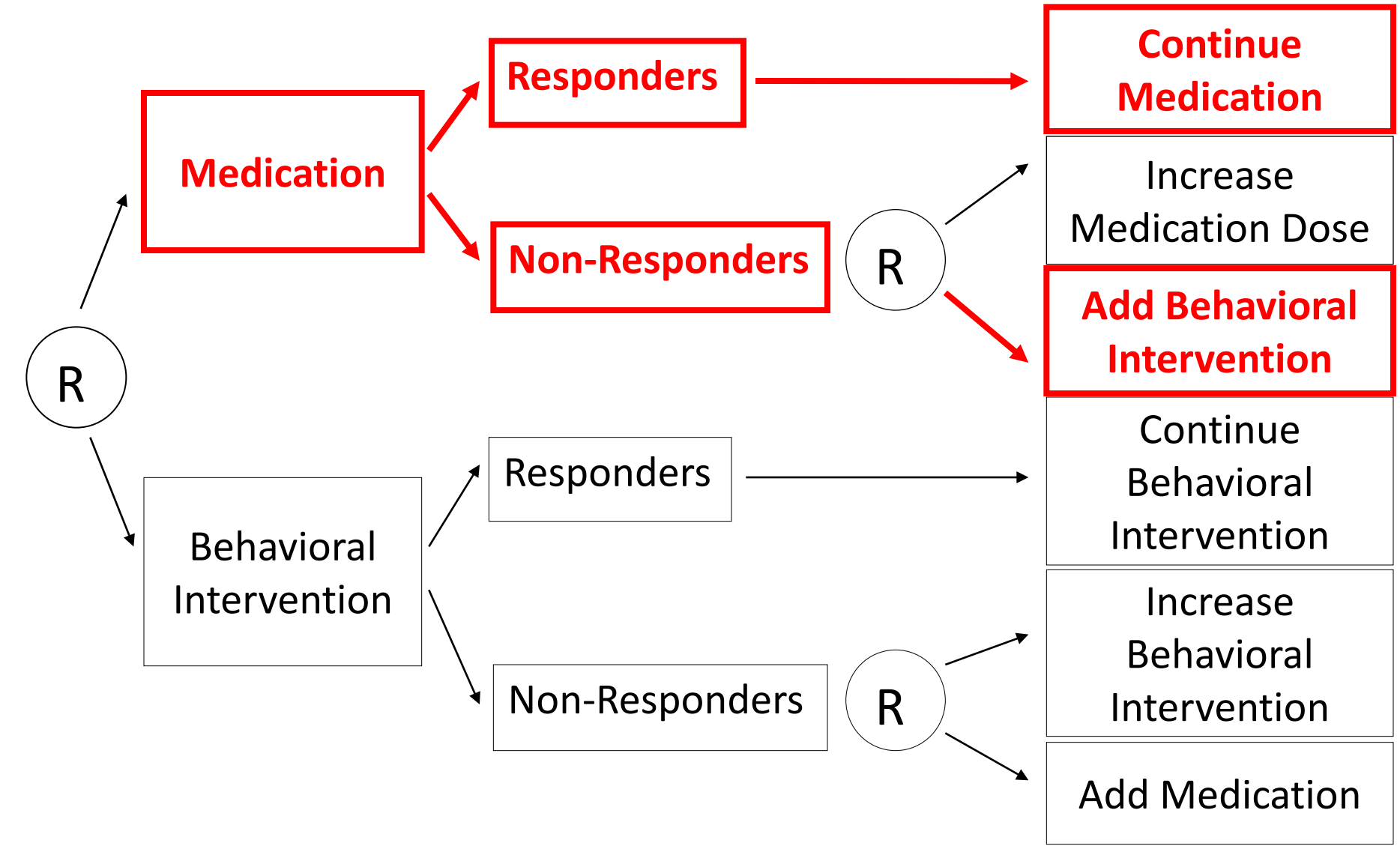
Review the ADHD SMART Design

Principal Investigator: Pelham



O1 — A1 — O2 / R Status — A2 — Y

There are 4 embedded adaptive treatment strategies in this SMART; **Here is one**



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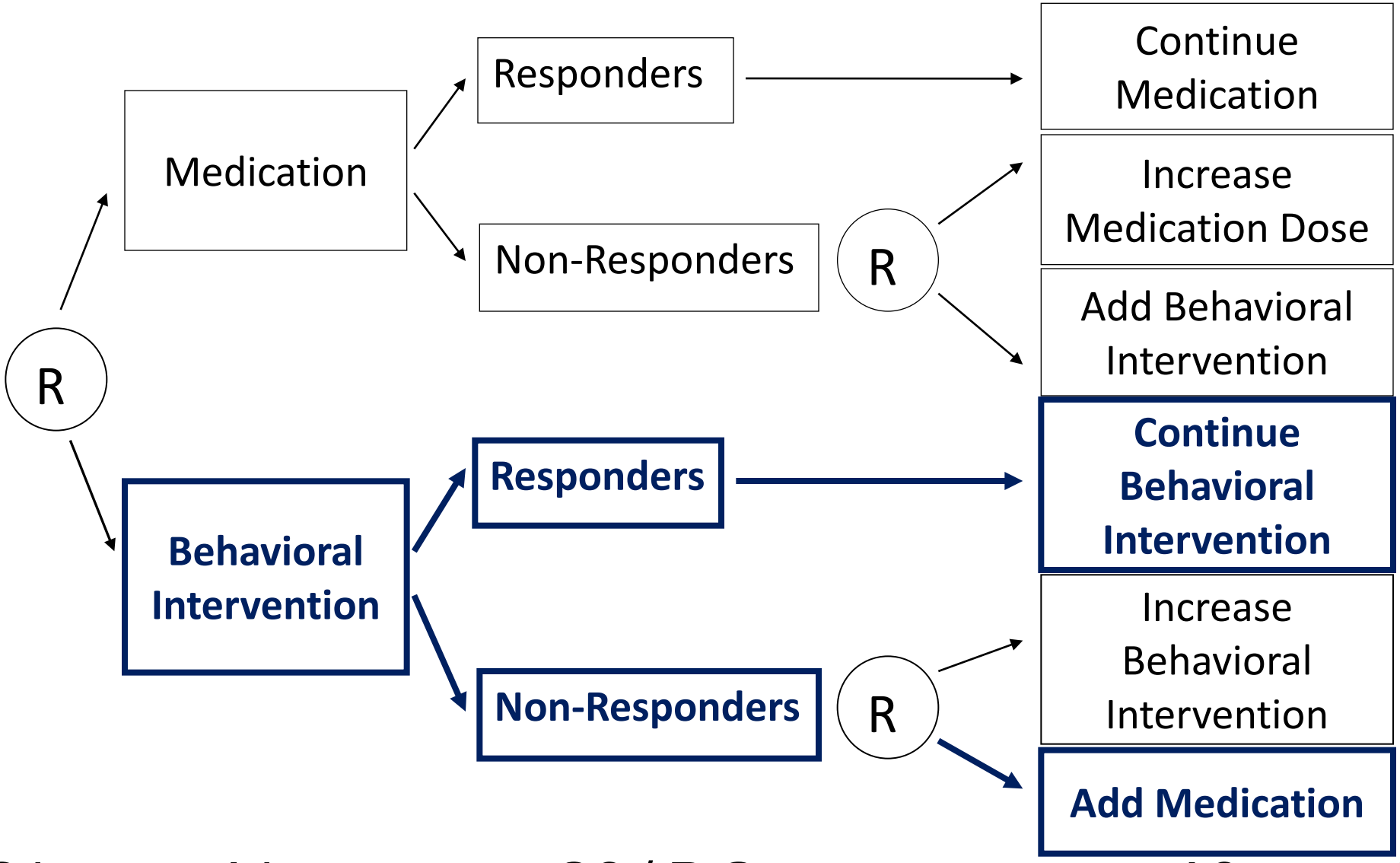


A subset of the data arising from a SMART may look like this

	ODD Dx	Baseline ADHD Score	Prior Med ?	First Line Txt	Resp /Non -resp	Second Line Txt	School Perfm
ID	O11	O12	O13	A1	R	A2	Y
1	0	-0.8066	0	-1 MED	1	.	2
2	1	-0.5339	0	-1	1	.	1
3	0	-1.0286	0	1 BMOD	1	.	3
4	0	-0.4216	0	-1	0	1 INTFY	4
5	0	-0.3682	0	-1	1	.	3
6	0	2.0927	1	1	0	-1 ADDO	4
7	0	0.0095	0	-1	1	.	1
8	0	0.4892	0	-1	0	1	5

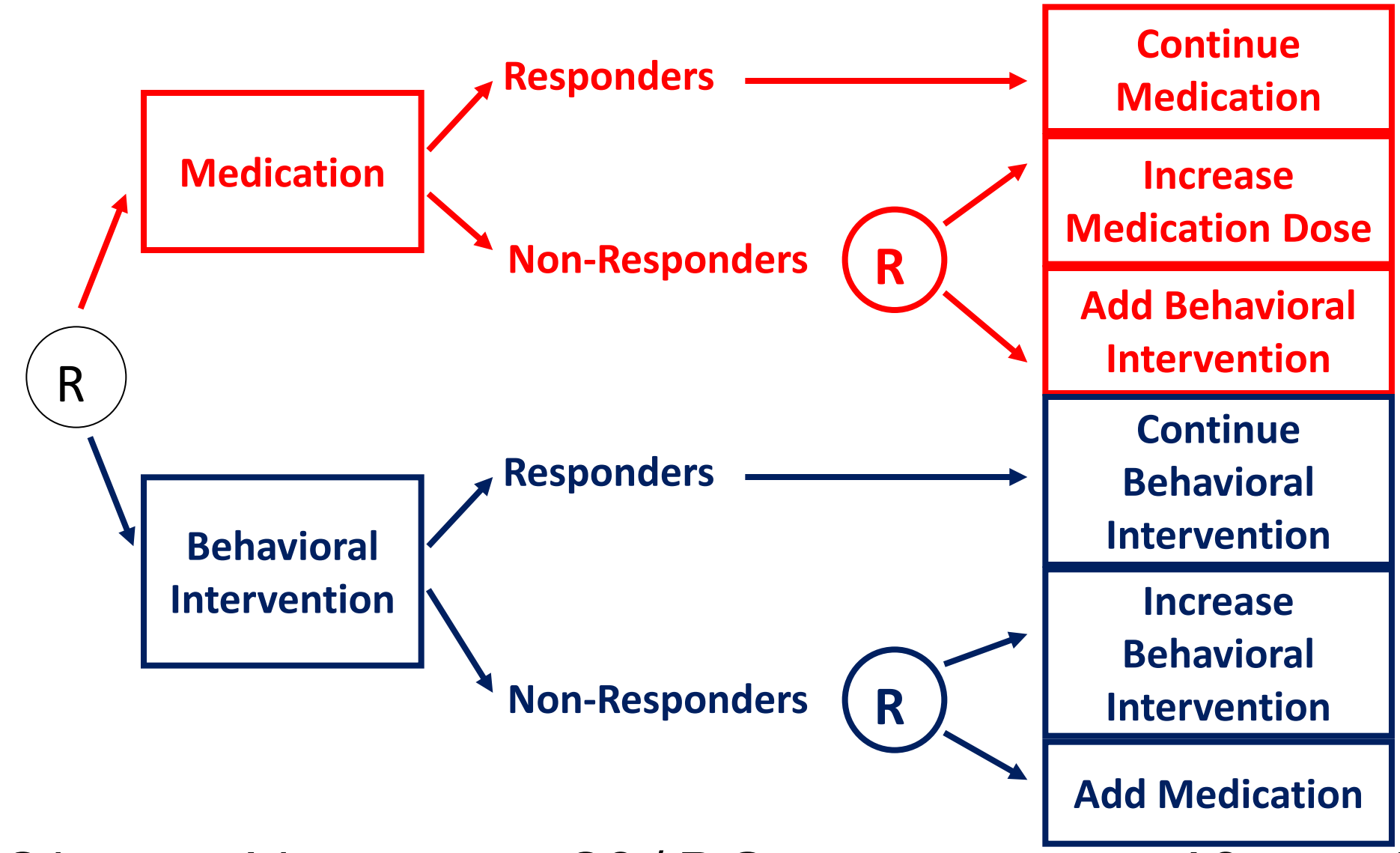
This is simulated data.

Typical Primary Aim 1: Main effect of first-line treatment?

- What is the best first-line treatment on average, controlling (by design) for future treatment?

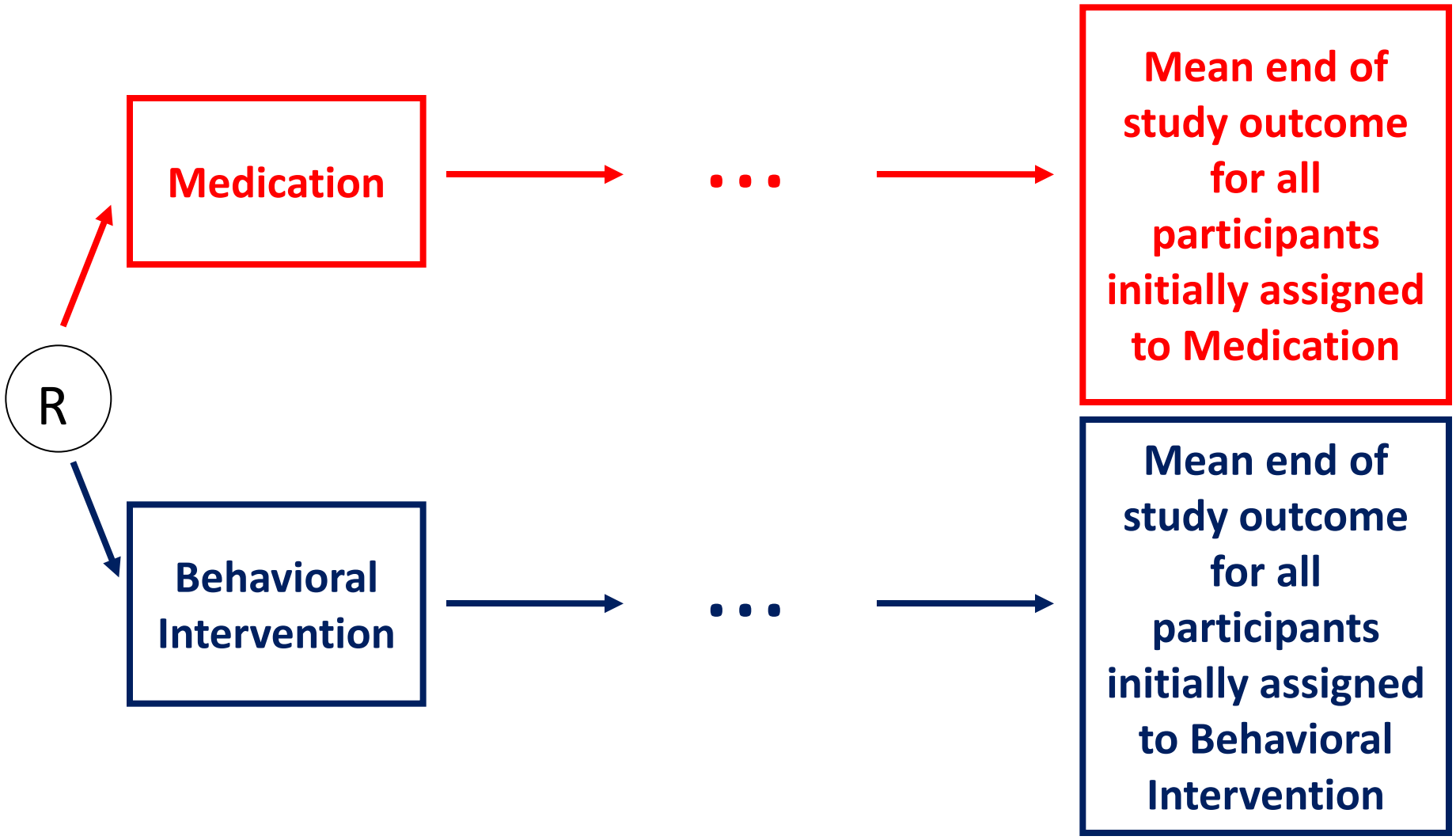
- Among children with ADHD, is it better in terms of end of study mean school performance, to begin treatment with a behavioral intervention or with medication?

Primary Question 1 is simply a comparison of two groups



O1 — A1 — O2 / R Status — A2 — Y

Primary Question 1 is simply a comparison of two groups



O1 —— A1 —— O2 / R Status —— A2 —— Y

SAS code for a 2-group mean comparison in end of study outcome

```
* center covariates prior to regression;
data dat1;
  set libdat.fakedata;
  o11c = o11 - 0.3266667;
  o12c = o12 - 0.0558753;
  o13c = o13 - 0.4533333;
run;
* run regression to get between groups difference;
proc genmod data = dat1;
  model y = a1 o11c o12c o13c;
  estimate 'Mean Y under BMOD' intercept 1 a1  1;
  estimate 'Mean Y under MED'  intercept 1 a1 -1;
  estimate 'Between groups difference'     a1  2;
run;
```

This analysis is with simulated data.

Primary Question 1 Results

Contrast Estimate Results

Label	Estimate	95% Conf Limits Lower	Upper	P-val
Mean Y under BMOD	3.4596	3.2624	3.6567	<.0001
Mean Y under MED	3.4604	3.2710	3.6498	<.0001
Between groups diff	0.0008	-0.2744	0.2727	0.9952

In this simulated data set/experiment, there is no average effect of first-line treatment. The mean outcome in both groups is around 3.45.

This analysis is with simulated data.

Or, here is the SAS code and results for the standard 2-sample t-test

```
data dat2; set dat1;
  if a1= 1 then a1tmp="BMOD";
  if a1=-1 then a1tmp="MED";
run;
proc ttest data=dat2;
  class a1tmp; var y;
run;
```

The TTEST Procedure Results

a1tmp	N	Mean	Std Dev	Std Err
BMOD	72	3.4722	1.1002	0.1297
MED	78	3.4487	0.7837	0.0887
Diff (BMOD-MED)		0.0235		0.1551

This analysis is with simulated data.

Typical Primary Question 2: Best of two adaptive interventions?

- In terms of average school performance, which is the best of the following two ATS:

First treat with medication, then

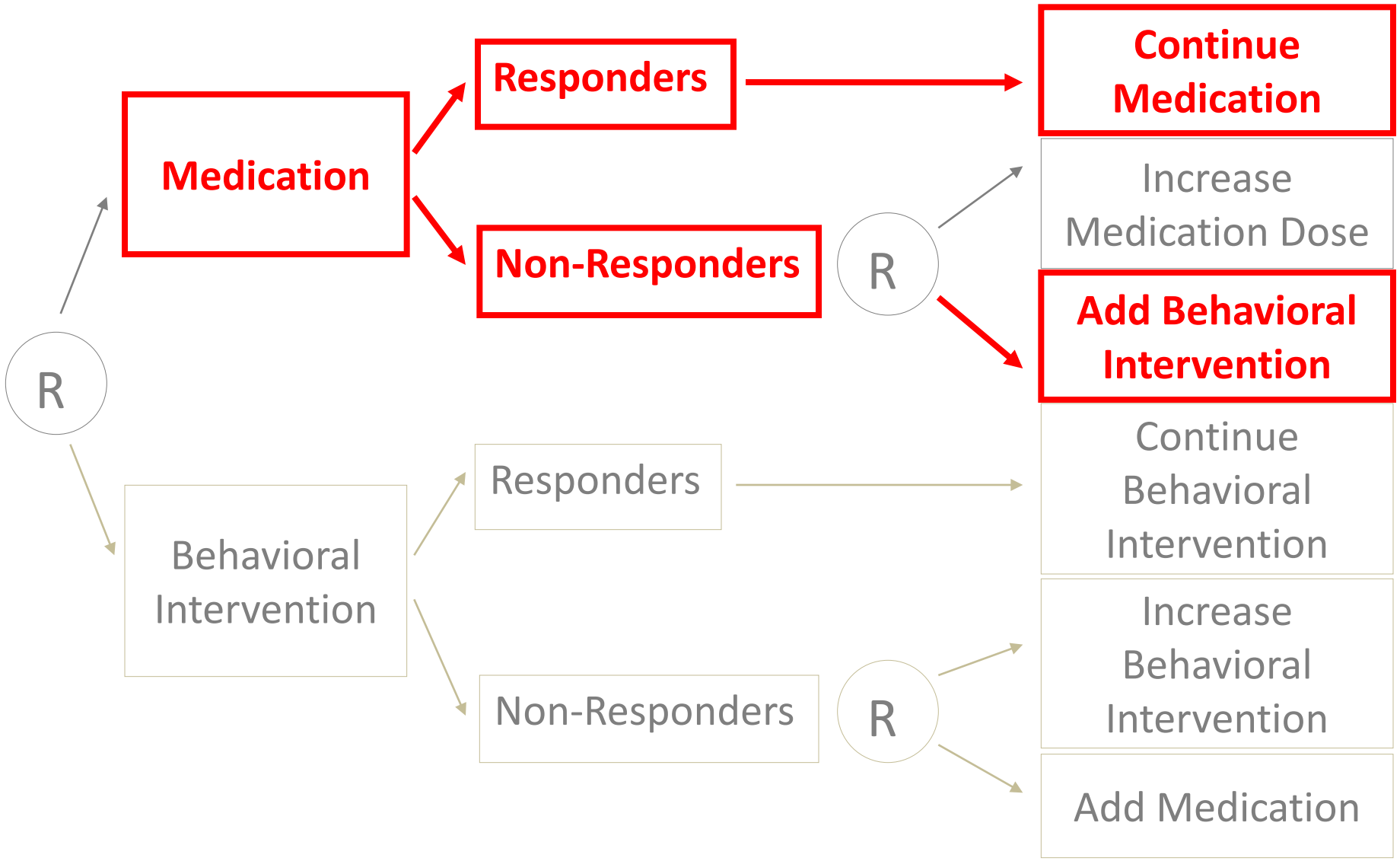
- **If respond, then continue treating with medication**
- **If non-response, then add behavioral intervention**

versus

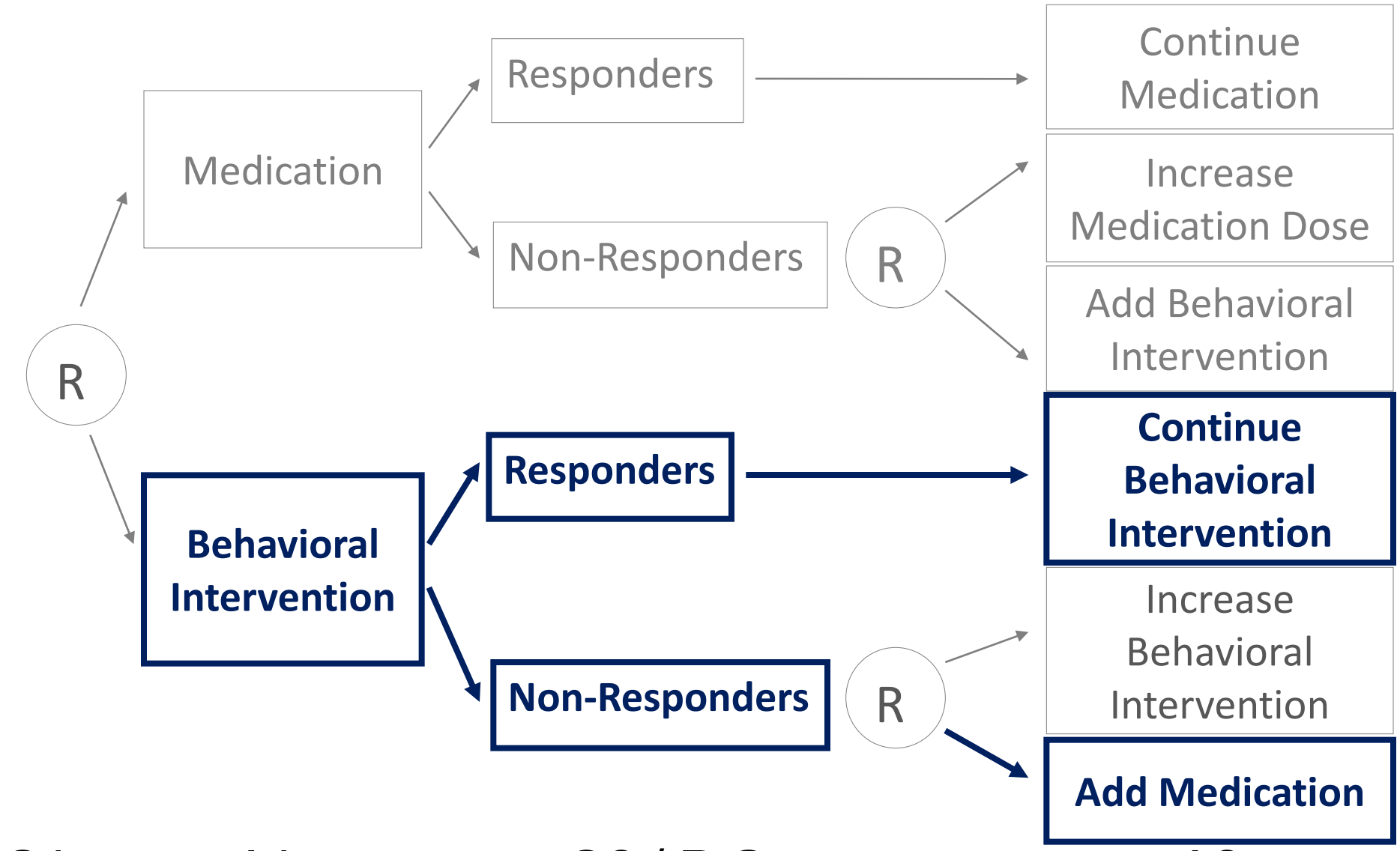
First treat with behavioral intervention, then

- **If response, then continue behavioral intervention**
- **If non-response, then add medication**

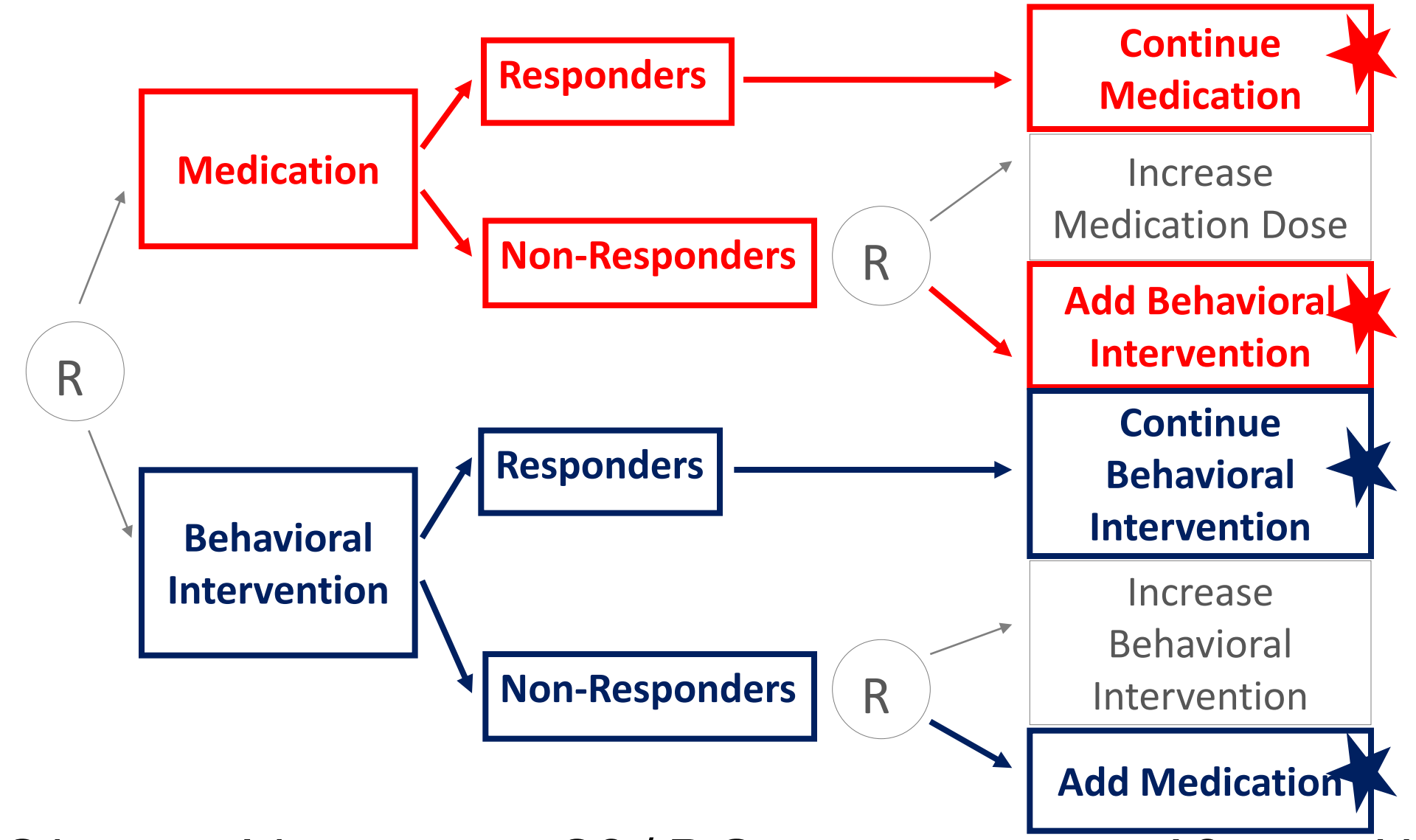
Comparison of mean outcome had population followed the red ATS versus…



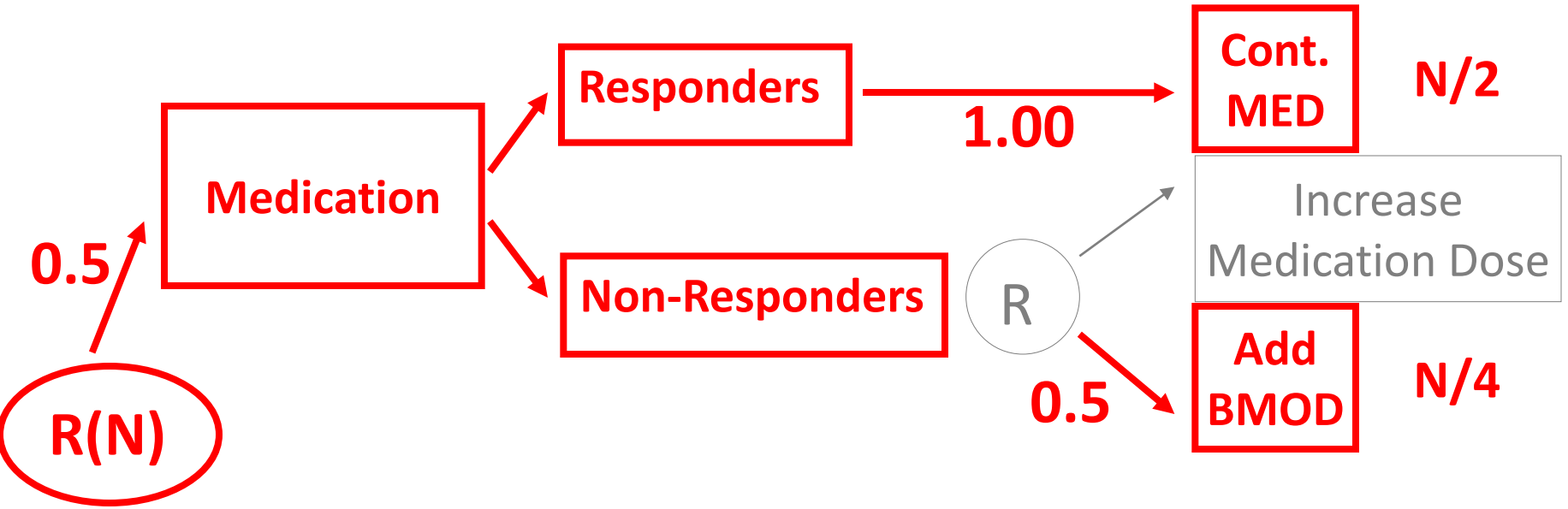
…versus the mean outcome had all population followed the blue ATS



But we cannot compare mean outcomes for participants in red versus those in blue.



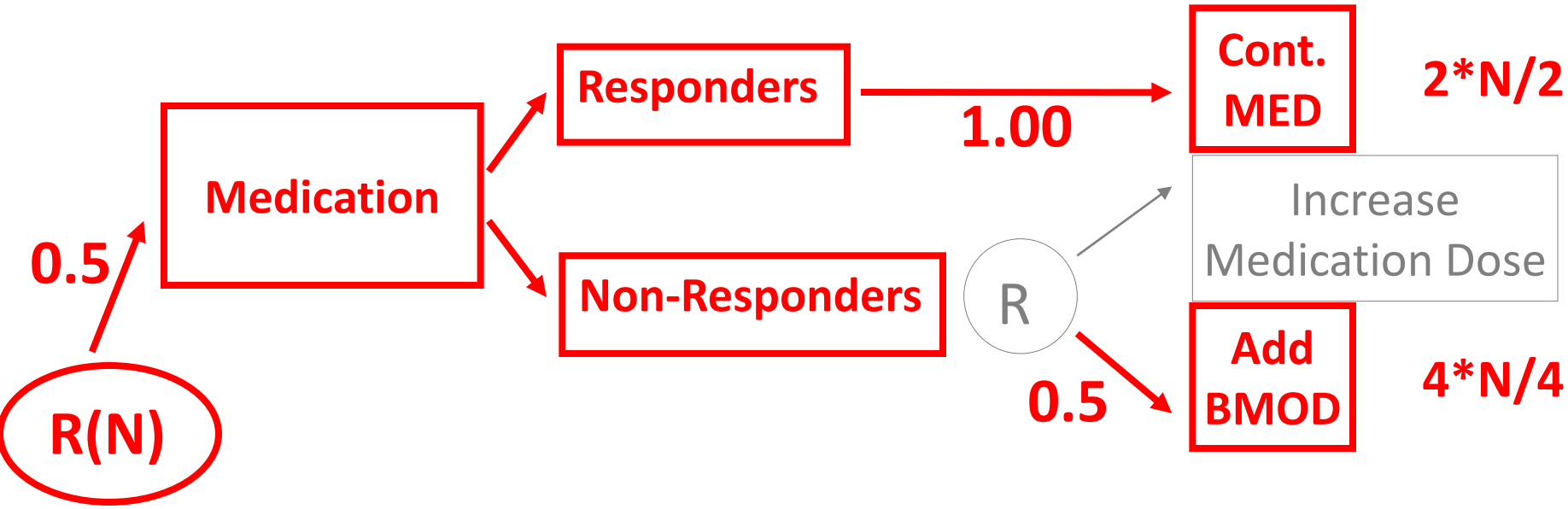
There is imbalance in the non/responding participants following the red ATS…



…because, by design,

- Responders to MED had a 0.5 = 1/2 chance of having had followed the red ATS, whereas
- Non-responders to MED only had a 0.5 x 0.5 = 0.25 = 1/4 chance of having had followed the red ATS

To estimate mean school performance had all participants followed the red ATS:



- Assign W = weight = 2 to responders to MED
- Assign W = weight = 4 to non-responders to MED
- Take W-weighted mean of sample who followed red ATS

SAS code to estimate mean outcome had all participants followed red ATS

```
* create indicator and assign weights;
data dat3; set dat2;
  Z1=-1;
  if A1*R=-1 then Z1=1; if (1-A1)*(1-R)*A2=-2 then Z1=1;
  W=4*R + 2*(1-R);
run;
* run W-weighted regression Y = b0 + b1*z1 + e;
* b0 + b1 will represent the mean outcome under red ATS;
proc genmod data = dat3;
  class id;
  model y = z1;
  scwgt w;
  repeated subject = id / type = ind;
  estimate 'Mean Y under red ATS' intercept 1 z1  1;
run;
```

This analysis is with simulated data.

Results: Estimate of mean outcome had population followed red ATS

Analysis Of GEE Parameter Estimates

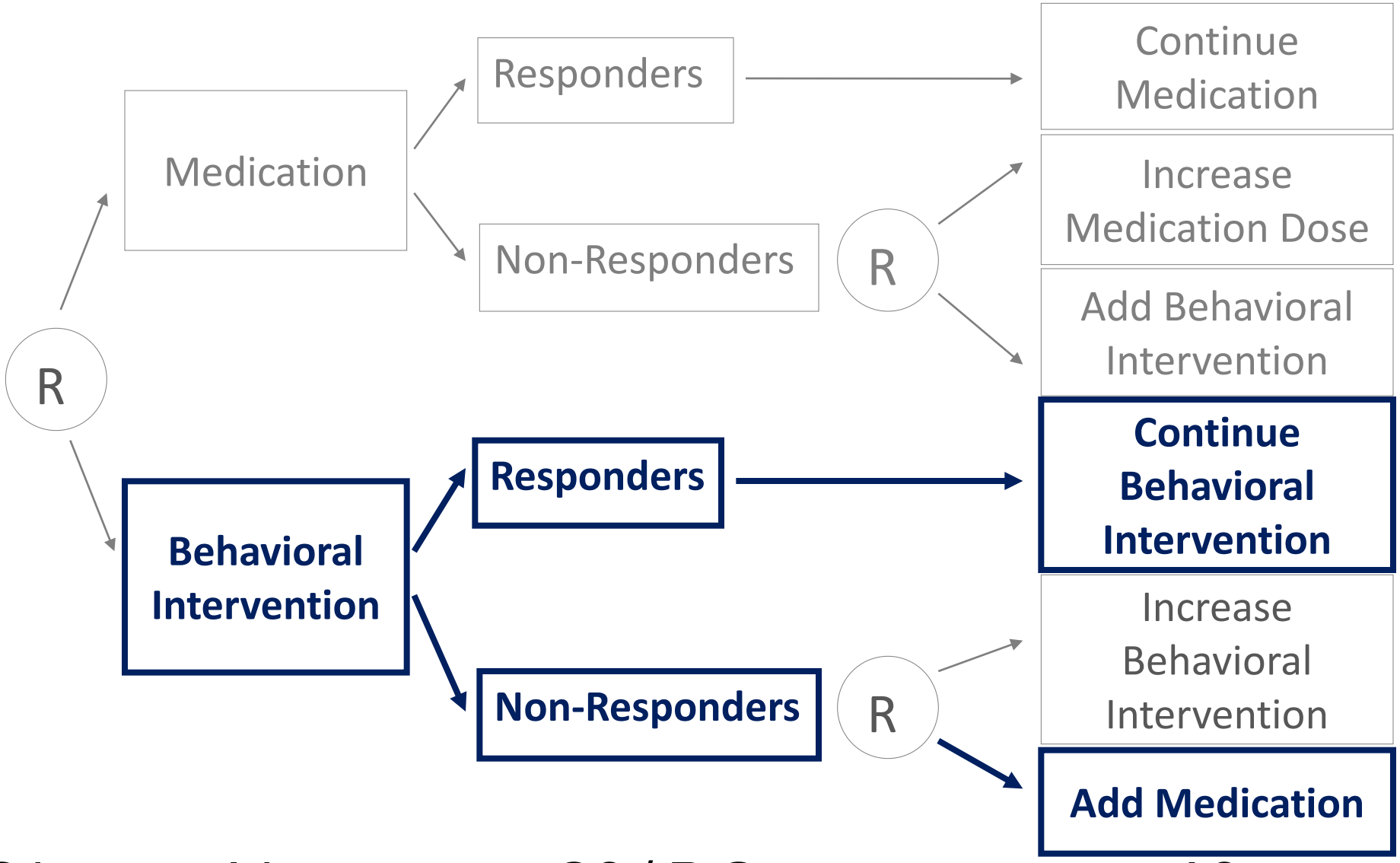
Parameter	Estimate	SError	P-value
Intercept	3.3590	0.0872	<.0001
Z1	-0.0168	0.0872	0.8468

Contrast Estimate Results

		95% Conf Limits		
	Estimate	Lower	Upper	SError
Mean Y under the red ATS	3.3421	3.0696	3.6146	0.1390

This analysis is with simulated data.

Similarly calculate the mean outcome had all participants followed the blue ATS



SAS code to estimate mean outcome had all participants followed blue ATS

```
* create indicator and assign weights;
data dat4; set dat2;
  Z2=-1;
  if A1*R= 1 then Z2=1; if (1+A1)*(1-R)*A2=-2 then Z2=1;
  W=4*R + 2*(1-R);
run;
* run W-weighted regression Y = b0 + b1*z2 + e;
* b0 + b1 will represent the mean outcome under blue ATS;
proc genmod data = dat4;
  class id;
  model y = z2;
  scwgt w;
  repeated subject = id / type = ind;
  estimate 'Mean Y under blue ATS' intercept 1 z2  1;
run;
```

This analysis is with simulated data.

Results: Estimate of mean outcome had population followed red ATS

Analysis Of GEE Parameter Estimates

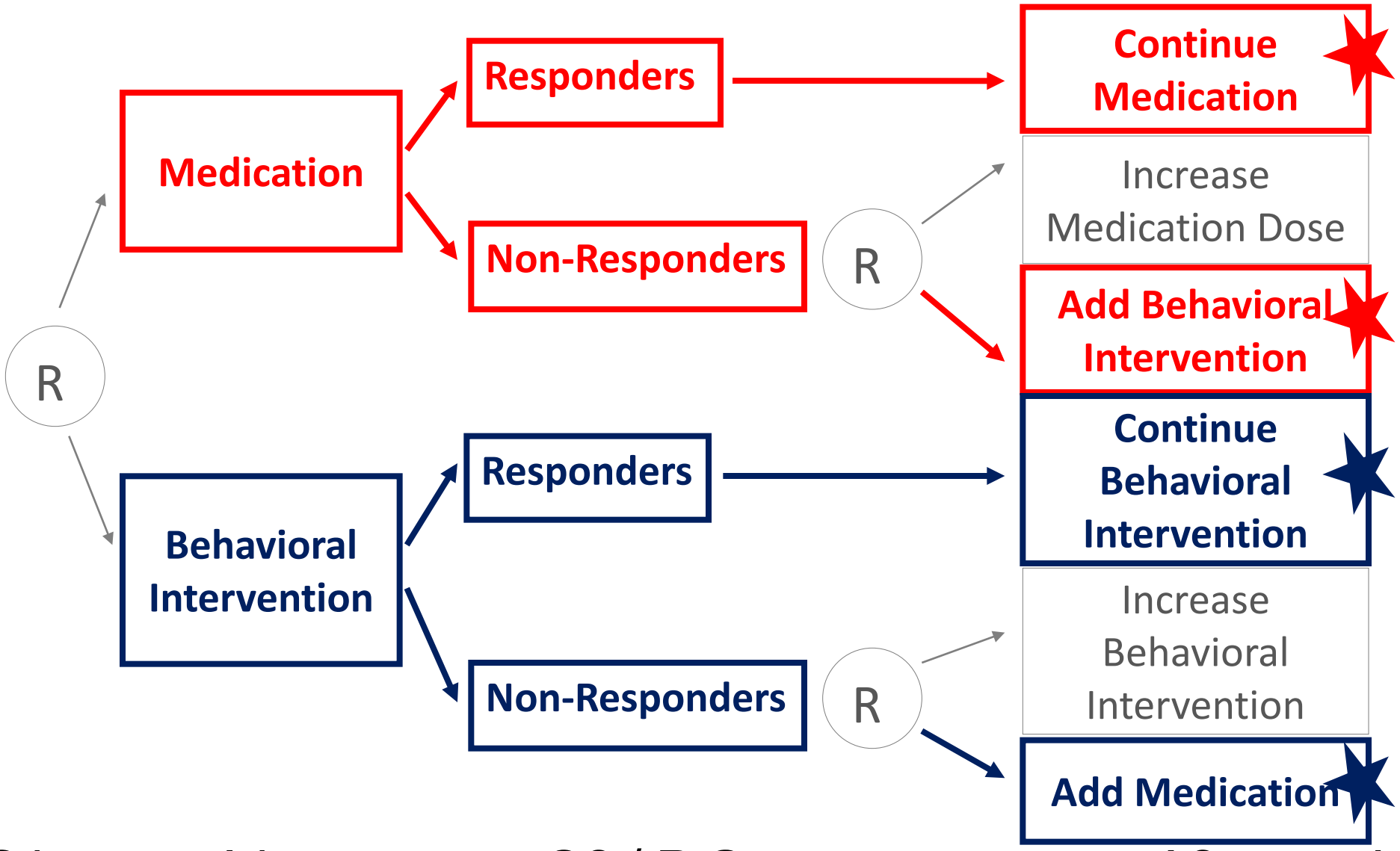
Parameter	Estimate	SError	P-value
Intercept	3.3049	0.1079	<.0001
Z2	-0.1356	0.1079	0.2089

Contrast Estimate Results

		95% Conf Limits		
	Estimate	Lower	Upper	SError
Mean Y under the blue ATS	3.1692	2.7799	3.5586	0.1987

This analysis is with simulated data.

What about a regression that allows us to compare the red and the blue ATS?



SAS code for a weighted regression to analyze Primary Question 2

```
data dat5; 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 dat6; set dat5; if Z1=1 or Z2=1 run;
proc genmod data = dat6;
  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;
```

A key step: This regression should be done only with the participants following the red and blue ATSs.

This analysis is with simulated data.

Primary Question 2 Results

Analysis Of GEE Parameter Estimates

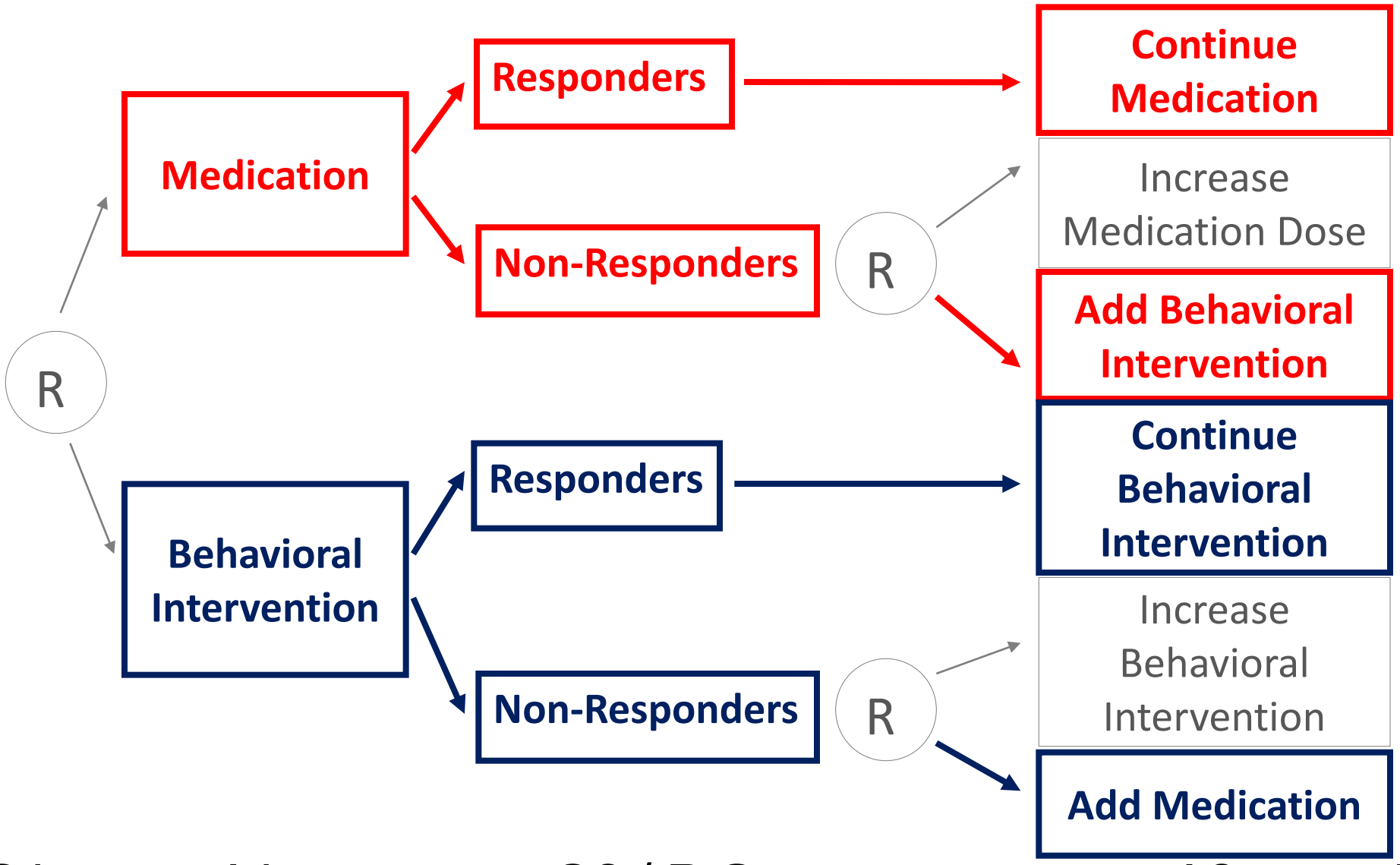
Parameter	Estimate	SError	P-value
Intercept	3.2557	0.1212	<.0001
Z2	0.0864	0.1212	0.4759

Contrast Estimate Results

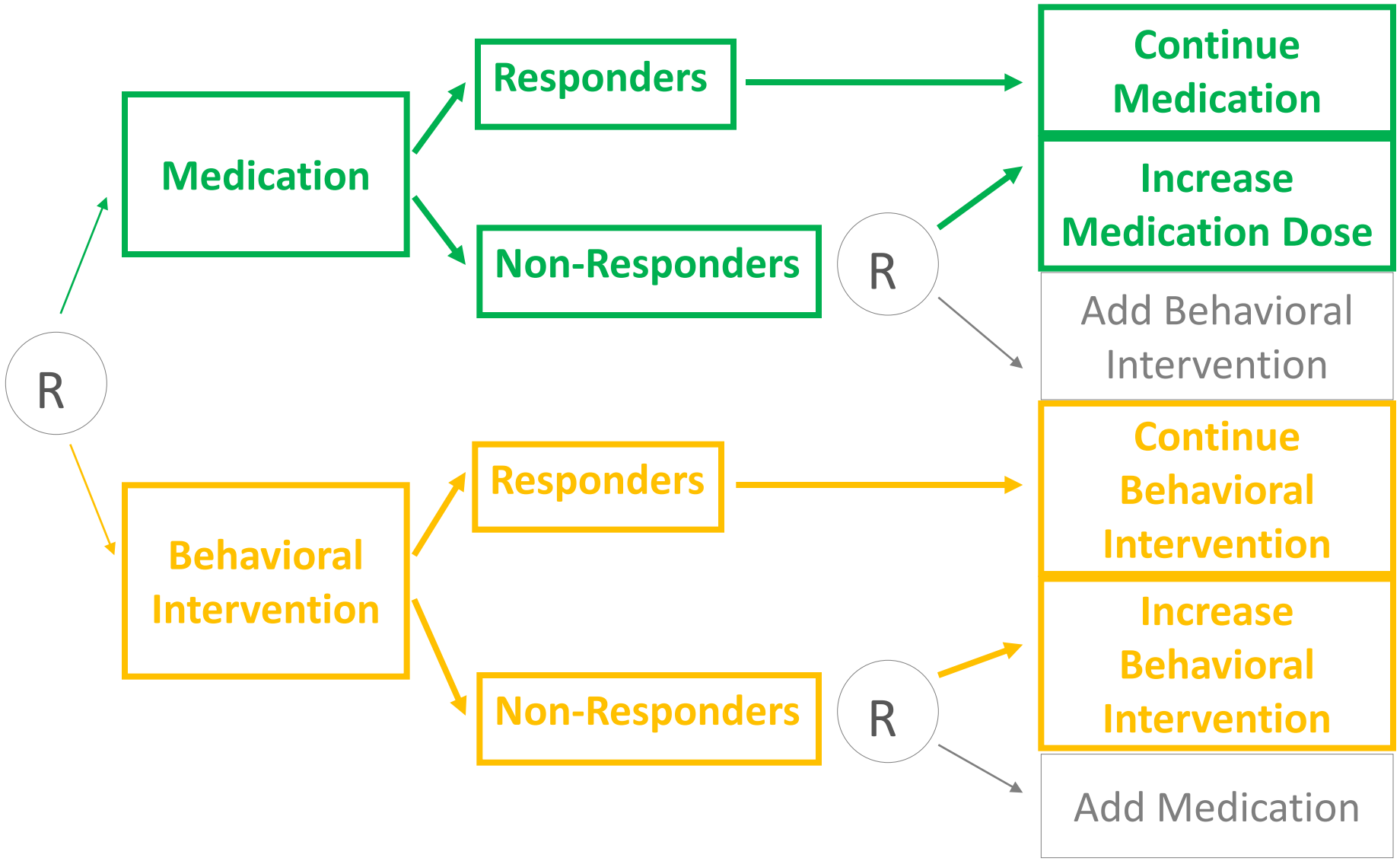
		Estimate	95% ConfLimits Lower	Upper	SError
Mean Y under red	ATS	3.3421	3.0696	3.6146	0.1390
Mean Y under blue	ATS	3.1692	2.7799	3.5586	0.1987
Diff: red - blue		0.1729	-0.3024	0.6481	0.2425

This analysis is with simulated data.

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?



SAS code for the regression to compare means under all four ATSs

```
data dat7; set dat2;
  * define weights and create responders replicates
  * (with equal "probability of getting A2");
  if R=1 then do;
    ob = 1; A2 =-1; weight = 2; output;
    ob = 2; A2 = 1; weight = 2; output;
    end;
  else if R=0 then do;
    ob = 1; weight = 4; output;
    end;
run;
```

This analysis is with simulated data.

SAG code for a weighted regression to estimate mean under all four ATSs

```
proc genmod data = dat7;
  class id;
  model y = a1 a2 a1*a2 o11 o12 o13;
  scwgt weight;
  repeated subject = id / type = ind;
  estimate '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'       a1 -2 a2  0 a1*a2  0;
  estimate '    Diff: orange - blue' int 0 a1  0 a2  2 a1*a2  2;
  * etc...;
run;
```

Increases statistical efficiency, leads to smaller standard errors, leads to smaller p-value.

This analysis is with simulated data.

Results: weighted regression method to estimate mean outcome under all 4 ATSs

Contrast Estimate Results

		Estimate	95% Conf Limits Lower	Upper	SError
Mean Y under red	ATS	3.1587	2.8692	3.6146	0.1477
Mean Y under blue	ATS	2.9317	2.5351	3.5586	0.2023
Mean Y under green	ATS	3.2555	3.0099	3.5586	0.1253
Mean Y under orange	ATS	3.4353	3.1683	3.5586	0.1362
Diff: red - blue		0.0236	-0.2502	0.6481	0.1397
Diff: orange - blue		0.5037	0.1474	0.8600	0.1818

This analysis is with simulated data.

Question, Answer, & Practice Exercise

Practice Exercise:

Write down the primary research aim for the SMART design you came up with in Module 2.

Do you need a weighting approach or a simple comparison in means to address this primary aim?

Secondary Aims Using Data Arising from a SMART

Getting SMART About Developing Individualized Sequences of Health Interventions

SBM, April 27

Daniel Almirall & Susan A. Murphy

Institute for Social Research
Survey Research Center
SRC

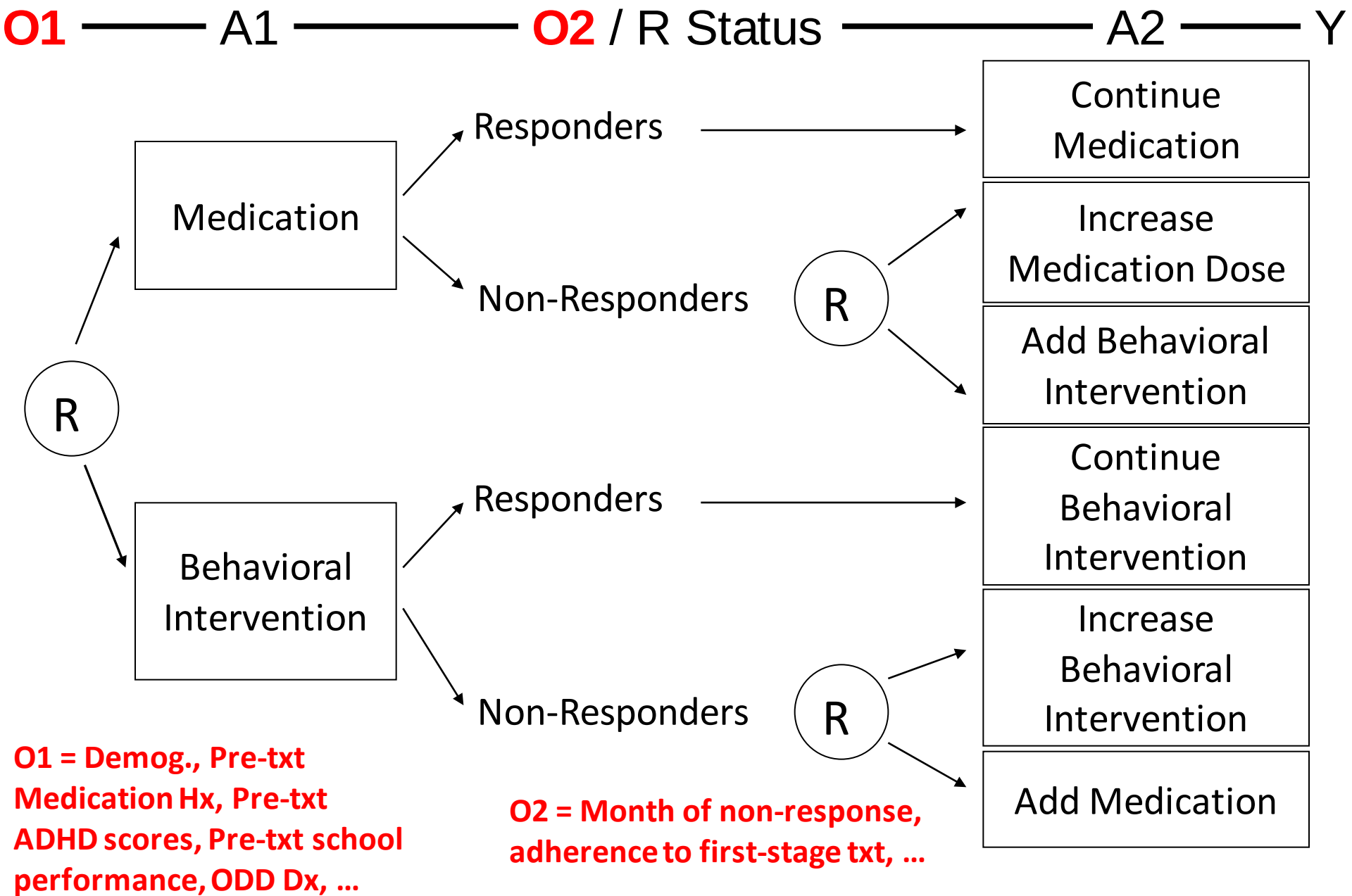
The Methodology Center

MICHIGAN
STATISTICS

Secondary Analyses Outline

- Auxiliary data typically in a SMART used for secondary aims?
- Typical secondary research questions (aims) in a SMART
- SAS code snippets
- Results from worked examples

Other Measures Collected in a SMART

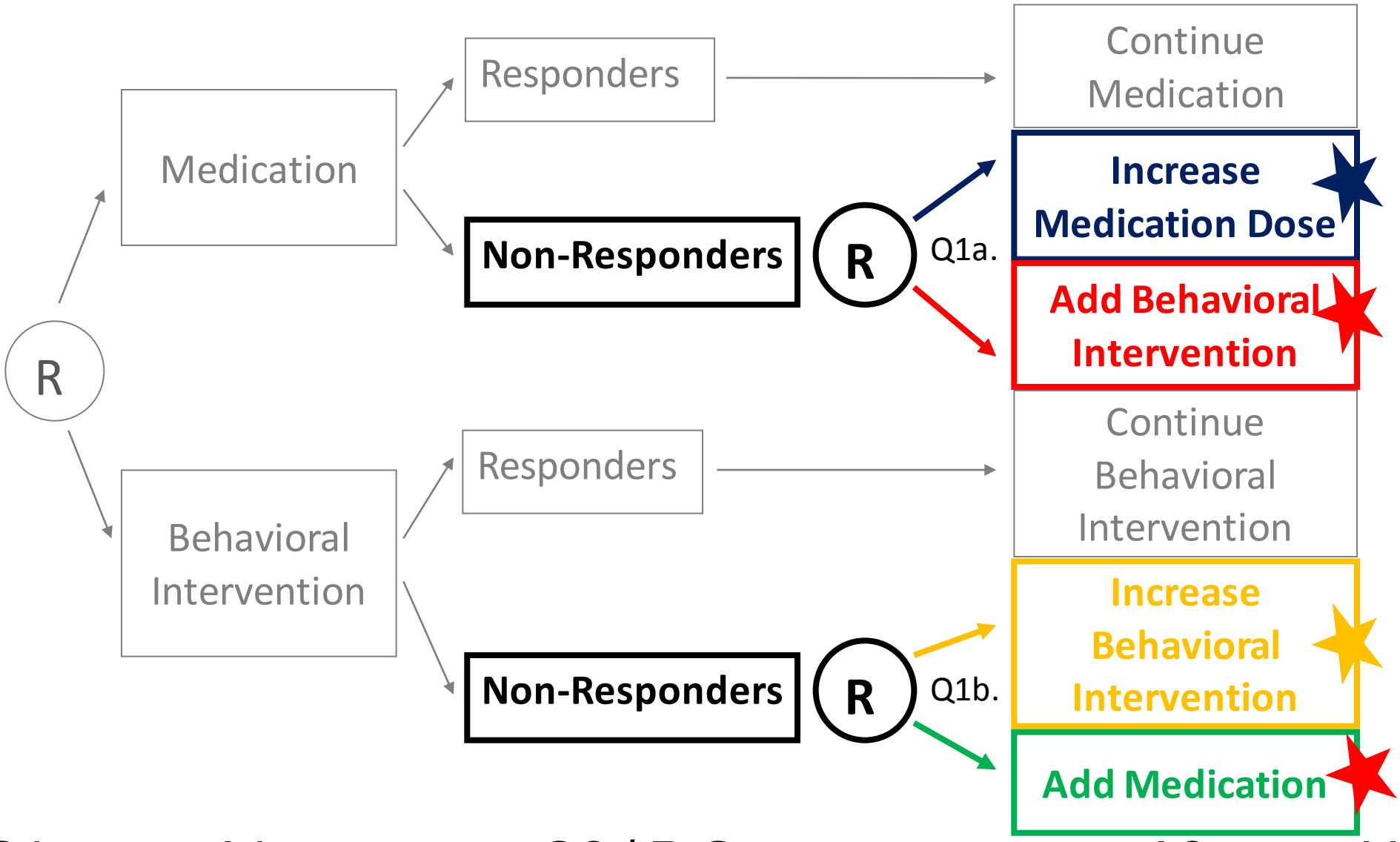


Typical Secondary Aim 1: Best second-line treatment?

a. Among children who do not respond to first-line medication, is it better to increase dosage or to add behavioral modification?

b. Among children who do not respond to first-line behavioral modification, is it better to increase intensity of behavioral treatment or to add medication?

Typical Secondary Aim 1: Best second-line treatment?



SAS code and results for Secondary Aim 1a: Second-line txt after MED

```
* use only medication non-responders;
data dat2;
  set dat1; if R=0 and A1=-1;
run;
* simple comparison to compare mean Y on add vs intensify (A2);
proc genmod data = dat2;
  model y = a2 o11c o12c o13c;
  estimate 'Mean Y w/INTENSIFY MED' intercept 1 a2  1;
  estimate 'Mean Y w/ADD BMOD'      intercept 1 a2 -1;
  estimate 'Between groups difference'          a2  2;
run;
```

Contrast Estimate Results

		95% Conf Limits		
Label	**Estimate**	**Lower**	**Upper**	**P-value**
Mean Y w/INTENSIFY MED	**3.5113**	**3.2318**	**3.7909**	**<.0001**
Mean Y w/ADD BMOD	**3.2385**	**2.9409**	**3.5360**	**<.0001**
Between groups difference	**0.2729**	**-0.1434**	**0.6891**	**0.1988**

This analysis is with simulated data.

SAS code and results for Secondary Aim 1b: Second-line txt after BMOD

```
* use only BMOD non-responders;
data dat3;
  set dat1; if R=0 and A1=1;
run;
* simple comparison to compare mean Y on add vs intensify (A2);
proc genmod data = dat3;
  model y = a2 o11c o12c o13c;
  estimate 'Mean Y w/INTENSIFY BMOD' intercept 1 a2  1;
  estimate 'Mean Y w/ADD MED'        intercept 1 a2 -1;
  estimate 'Between groups difference'           a2  2;
run;
```

Contrast Estimate Results

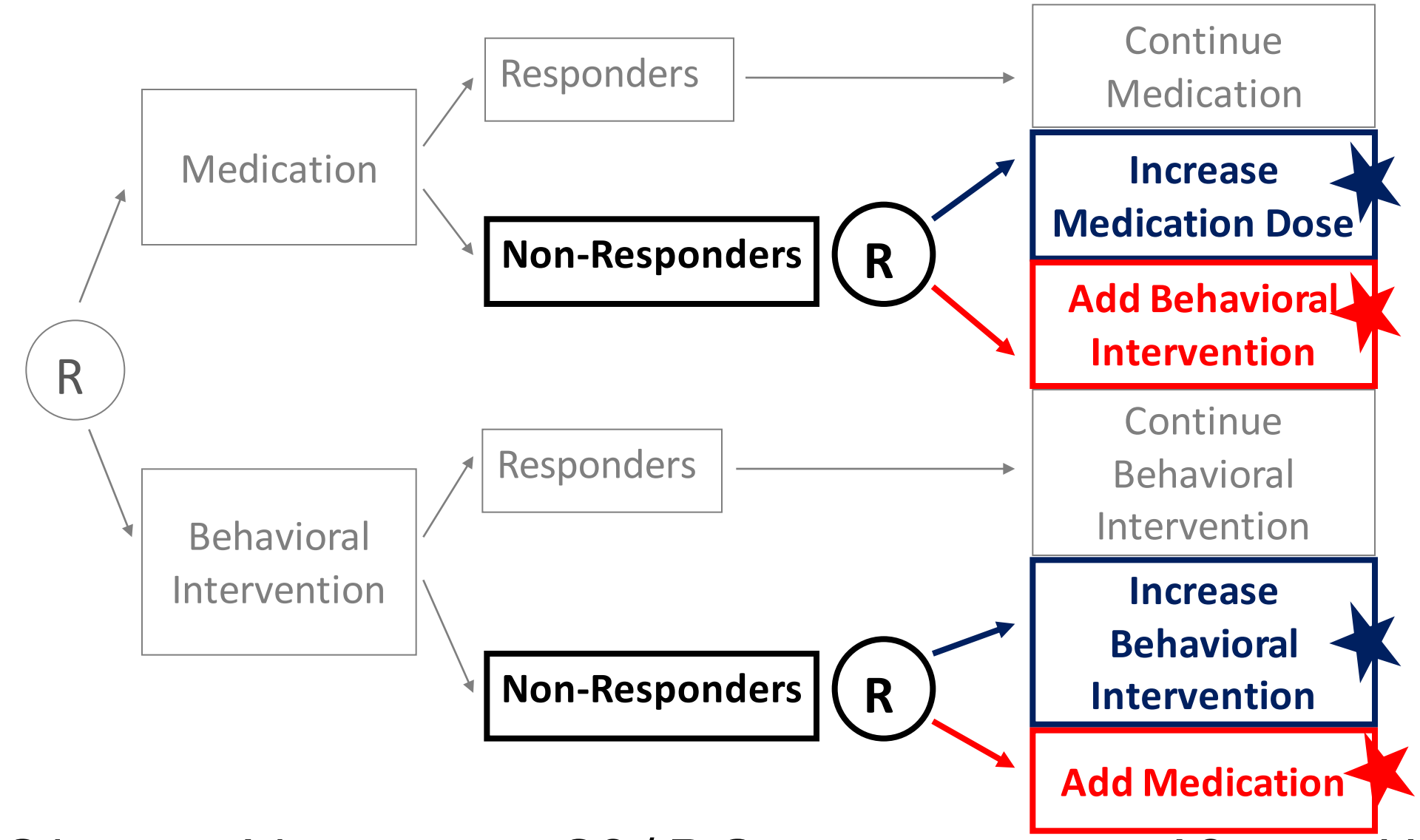
		95% Conf Limits		
Label	**Estimate**	**Lower**	**Upper**	**P-value**
Mean Y w/INTENSIFY BMOD	**3.5042**	**3.1628**	**3.8456**	**<.0001**
Mean Y w/ADD MED	**2.1412**	**1.6808**	**2.6016**	**<.0001**
Between groups difference	**1.3630**	**0.8069**	**1.9192**	**<.0001**

This analysis is with simulated data.

Typical Secondary Aim 2: Best second-line tactic?

- Among children who do not respond to (either) first-line treatment, is it better to increase initial treatment or to add a different treatment to the initial treatment?

Typical Secondary Aim 2: Best second-line tactic?



O1 — A1 — O2 / R Status — A2 — Y

SAS code and results for Secondary Aim 2: Second-line tactic

```
* use only non-responders;
data dat4;
  set dat1; if R=0;
run;
* simple comparison to compare mean Y on add vs intensify (A2);
proc genmod data = dat4;
  model y = a2 o11c o12c o13c;
  estimate 'Mean Y w/INTENSIFY tactic' intercept 1 a2  1;
  estimate 'Mean Y w/ADD TXT tactic'   intercept 1 a2 -1;
  estimate 'Between groups difference'             a2  2;
run;
```

Contrast Estimate Results

		95% Conf Limits		
Label	**Estimate**	**Lower**	**Upper**	**P-value**
Mean Y w/INTENSIFY tactic	**3.5046**	**3.2541**	**3.7552**	**<.0001**
Mean Y w/ADD TXT tactic	**2.8568**	**2.5601**	**3.1536**	**<.0001**
Between groups difference	**0.6478**	**0.2580**	**1.0376**	**0.0011**

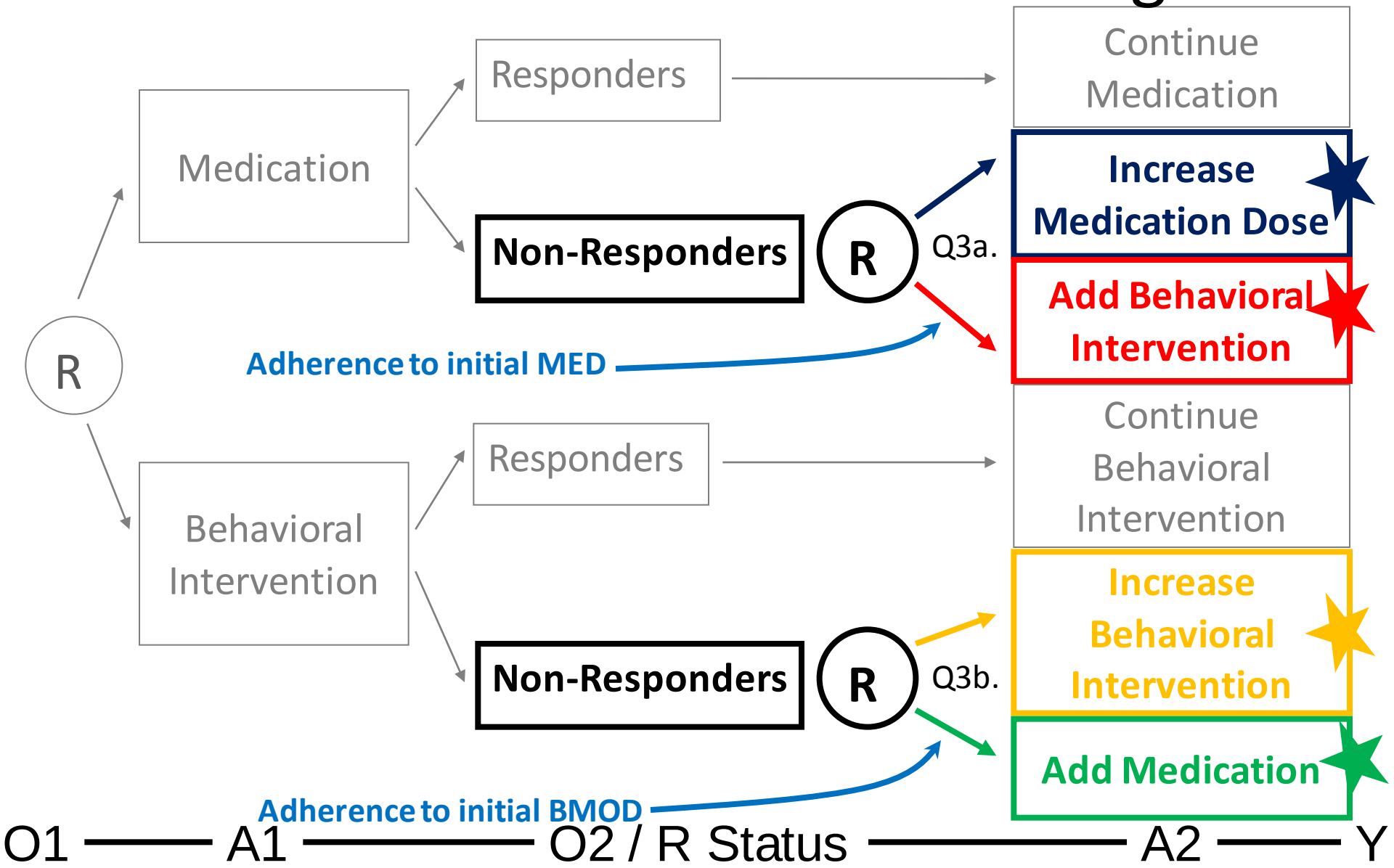
This analysis is with simulated data.

Typical Secondary Aim 3: Second-line treatment tailoring?

a. Does adherence to first-line MED strongly moderate the impact of increasing MED dosage versus adding BMOD?

b. Does adherence to first-line BMOD strongly moderate the impact of intensifying BMOD versus adding MED?

Typical Secondary Aim 3: Second-line treatment tailoring?



SAS code and results for Secondary Aim 3: Second-line treatment tailoring

```
* use only non-responders;
data dat5; set dat1; if R=0; run;

* comparison of add vs intensify given first line txt and adherence;
proc genmod data = dat5;
  model y = o11c o12c o13c a1 a1*o11c o21c o22 a2 a2*a1 a2*o22;
  * effect of add vs intensify given first-line = MED x ADH status;
  estimate 'INT vs ADD for NR MED ADH'     a2 2 a2*a1 -2 a2*o22  2 ;
  estimate 'INT vs ADD for NR MED Non-ADH' a2 2 a2*a1 -2 a2*o22  0 ;
  * effect of add vs intensify given first-line = BMOD x ADH status;
  estimate 'INT vs ADD for NR BMOD ADH'     a2 2 a2*a1 2 a2*o22  2 ;
  estimate 'INT vs ADD for NR BMOD Non-ADH' a2 2 a2*a1 2 a2*o22  0 ;
run;
```

Contrast Estimate Results

Label	Estimate	95% Conf Limits Lower	Upper	P-value
INT vs ADD for NR MED ADH	0.8971	0.4396	1.3547	0.0001
INT vs ADD for NR MED Non-ADH	-0.3006	-0.8020	0.2008	0.2399
INT vs ADD for NR BMOD ADH	1.4812	1.0254	1.9371	<.0001
INT vs ADD for NR BMOD Non-ADH	0.2835	-0.3693	0.9363	0.3947

This analysis is with simulated data.

Typical Secondary Aim 4: A more deeply individualized ATS via Q-learning

Q-Learning is an extension of regression to sequential treatments.

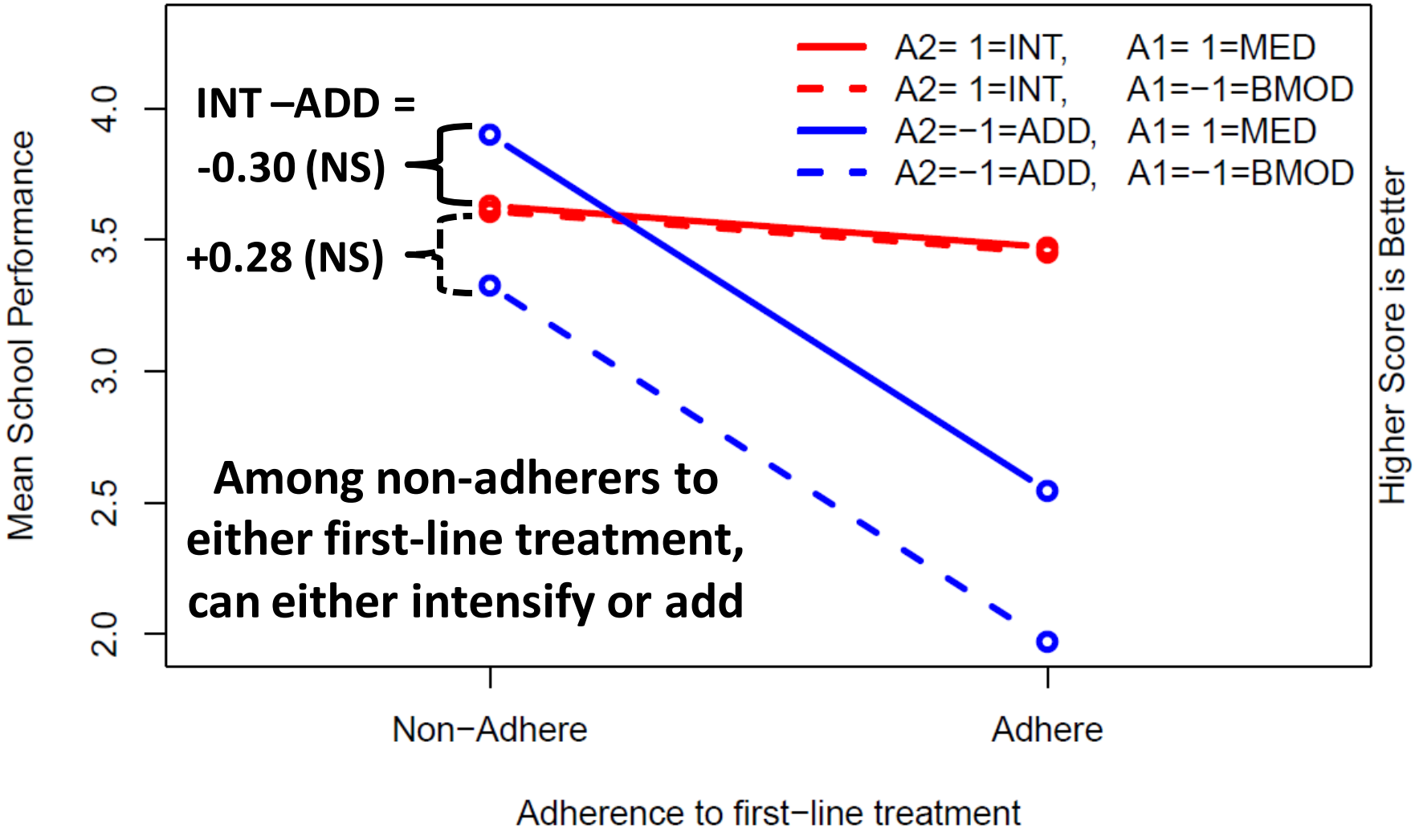
- This approach results in a proposal for an optimal adaptive treatment strategy.
- A subsequent trial would evaluate the proposed adaptive treatment strategy.

Steps in Q-Learning Regression

Work backwards (reverse-engineering!)

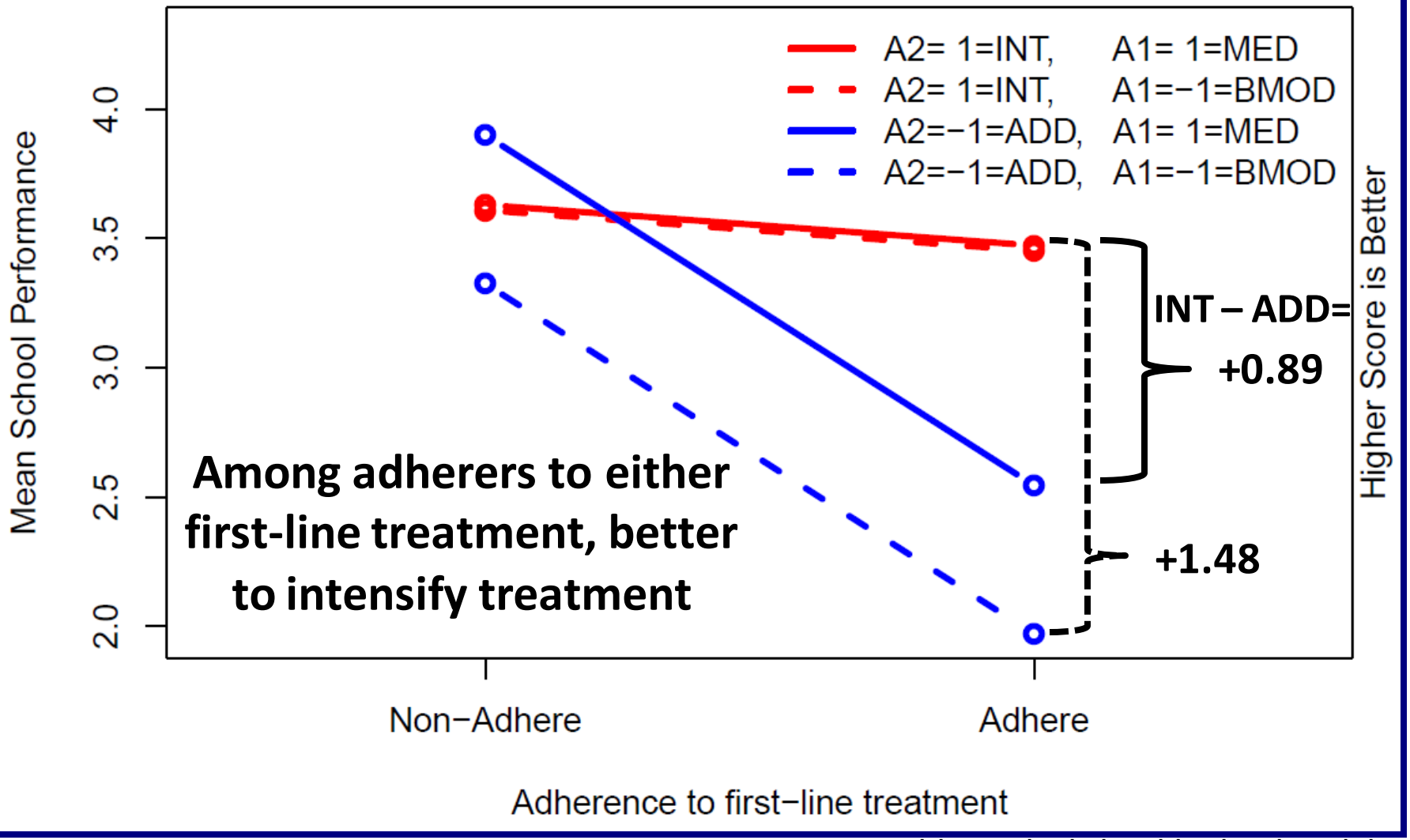
1. Do a regression to learn about the optimal second-line treatment **We already did this for Aim 3!**
   - Assign each non-responder $\hat{Y}_i$, an estimate of the outcome under optimal second-line treatment
2. Using $\hat{Y}_i$ do a regression to learn about the optimal first-line treatment

Q-Learning Step 1: Learn optimal second-line treatment for non-responders



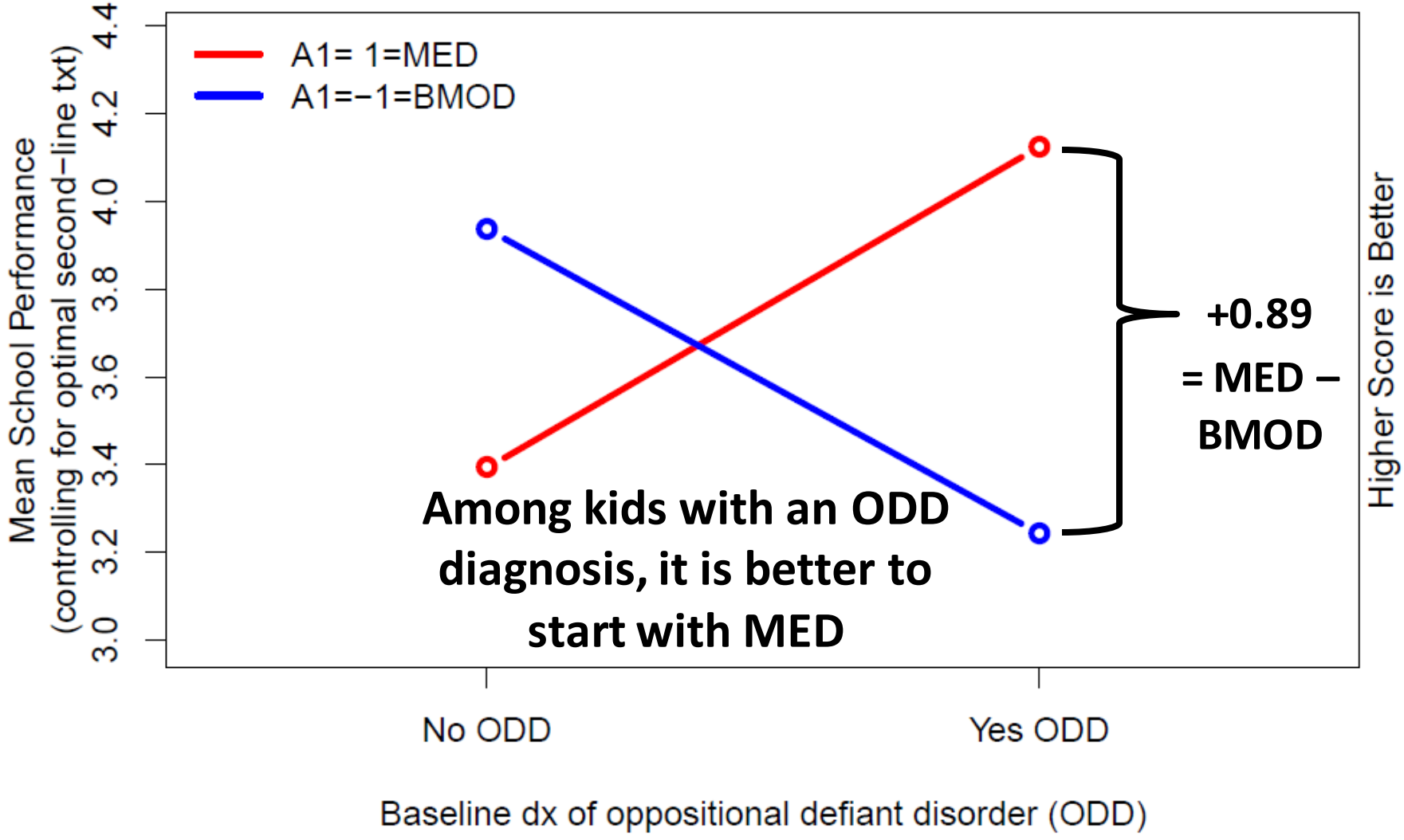
This analysis is with simulated data.

Q-Learning Step 1: Learn optimal second-line treatment for non-responders



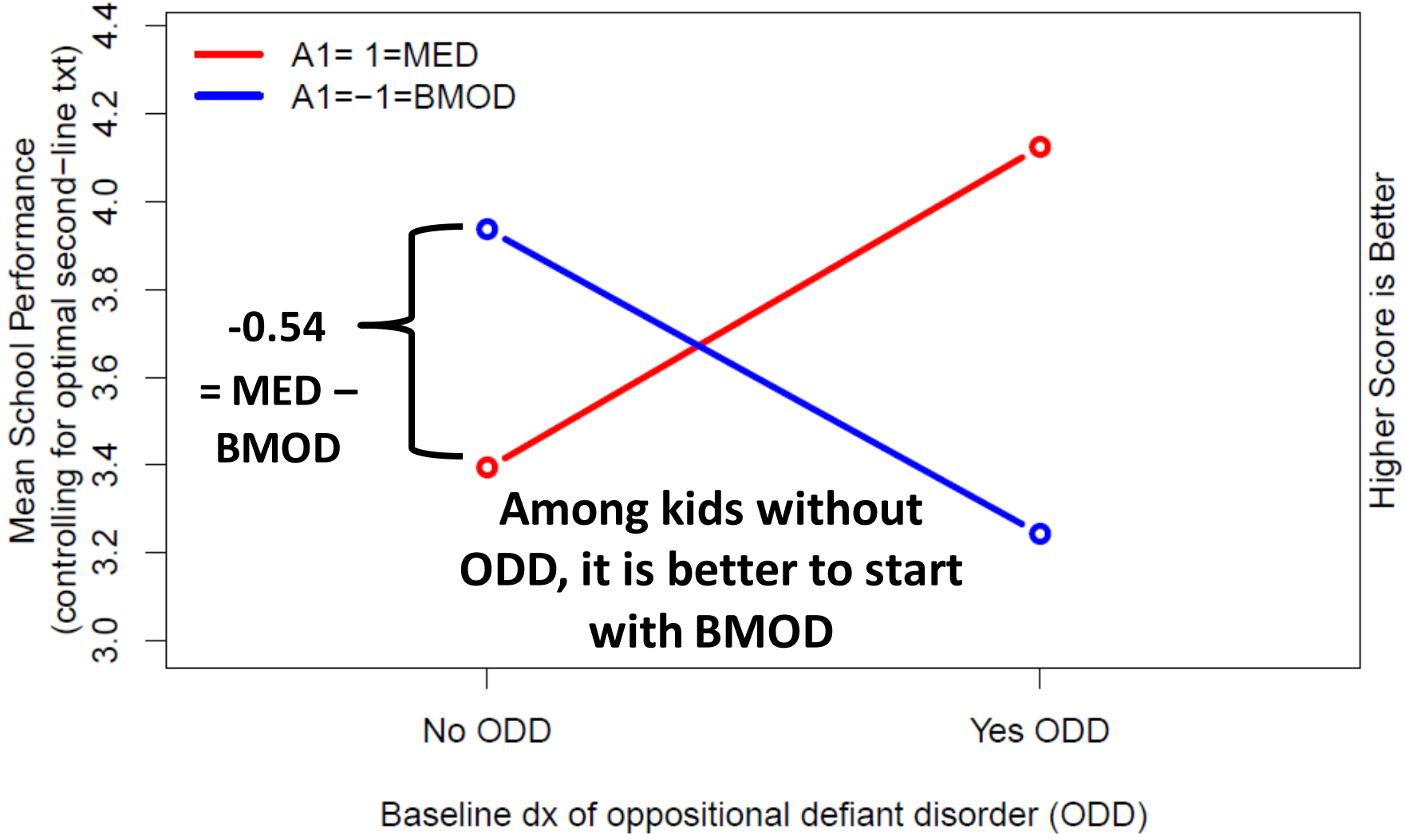
This analysis is with simulated data.

Q-Learning Step 2: Learn optimal first-treatment for all given optimal future txt



This analysis is with simulated data.

Q-Learning Step 2: Learn optimal first-treatment for all given optimal future txt



This analysis is with simulated data.

What did we learn with Q-learning?

Adaptive Treatment Strategy Proposal

- If the child has an ODD diagnosis, then begin with MED; otherwise, begin with BMOD.

- If the child is non-responsive and non-adherent to either first-line treatment, then ADD or INTENSIFY treatment.
- If the child is non-responsive but adherent to either first-line treatment, then it is better to INTENSIFY first-line treatment.
- If the child is responsive to first-line treatment, then CONTINUE first-line treatment.

This Q-learning analysis was done with simulated/altered data.

Thank you.

- Software for Q-learning is now available in R and it is coming out soon for SAS! Visit:

methodology.psu.edu/ra/adap-treat-strat/qlearning

- These slides are posted at

www.stat.lsa.umich.edu/~samurphy/nida/SBM2011Slides.pdf

Question, Answer, & Practice Exercise

Practice Exercise:

Write down a secondary research aim for the SMART design you came up with in Module 2.

Who is included in the data analysis corresponding to this research question?