ADAPTIVE TREATMENT STRATEGIES AND *SMART* STUDIES

R. L. Brown, Ph.D.
School of Nursing
University of Wisconsin

INTERVENTION DEVELOPMENT

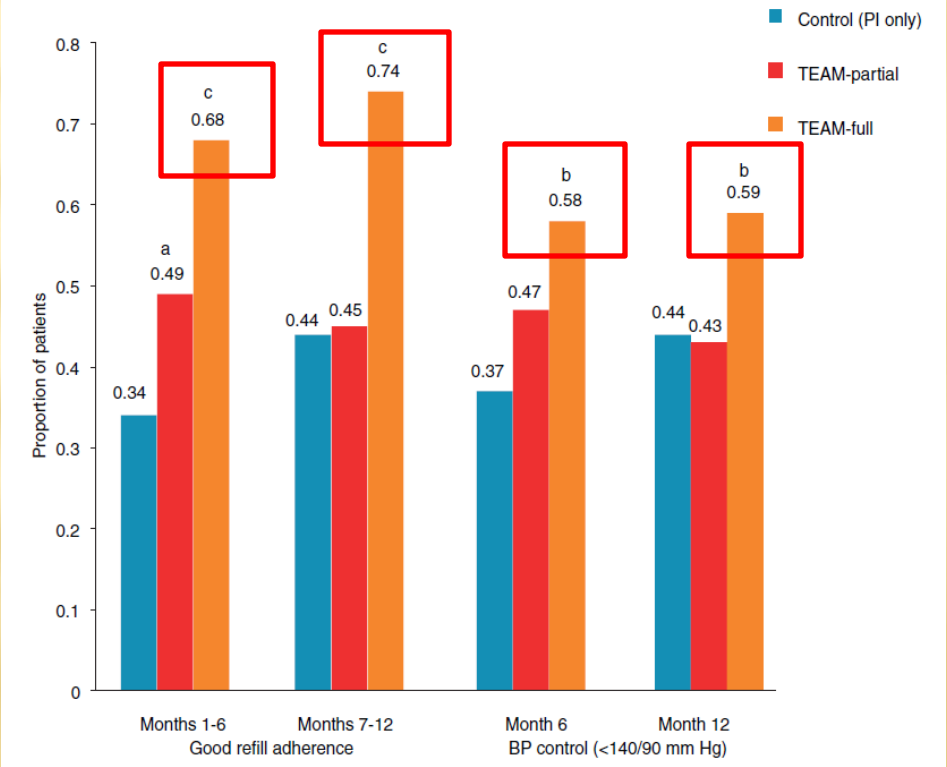
"The traditional approach to intervention development has involved constructing an intervention a priori and then evaluating it in a standard randomized controlled trial (RCT). After the RCT, post hoc analyses are done to help explain how the intervention worked, or why it did not work. The results of these analyses may be used to refine the intervention program and construct a second generation version of the program, which is then evaluated in a new RCT." (Collins, Murphy, and Strecher, 2007).

SHORTCOMINGS OF THIS APPROACH

- Post-hoc – not planned does not follow an RCT
- Reduced power
- Sometimes it can be useful

POST-HOC ANALYSIS

Svarstad, B. L., Kotchen, J. M., Shireman, Brown, R. L., T. I., Crawford, Mount, J. K., Palmer, P., Vivian, E., and Wilson, D. (2013). Improving refill adherence and hypertension control in black patients: Wisconsin TEAM trial. *J. Am Pharm Assoc*. 53:5, 30-39, doi: 10.1331/JAPhA.2013.12246.



FIXED VS. ADAPTIVE INTERVENTIONS

- Fixed Intervention strategies: "one size fits all"

  Confirmatory

  The same dose or type of services are offered to all subjects.

  No adjustment over time – you leave it alone!

- Adaptive interventions: sequential processes

  Exploratory - developmental

  The dose or type of services are individualized based on subjects' characteristics or clinical presentation.

  Adjustment over time in response to ongoing performance.

EXAMPLE OF REAL WORLD PROBLEM

An investigator seeking an R01

At 26 weeks, no statistically significant differences were noted between the groups in opioid dose (d=0.03, p=0.84). However, several participants in both groups were noted to change (reduce or increase) opioid use, as expressed by the morphine-equivalent dose used in the 'past 28 days' (maximum decrease: 6,743mg in a treatment participant; maximum increase: 2,680mg in a control participant). **Overall, this pilot confirmed methods feasibility and intervention acceptability, and the potential for treatment to improve outcomes in opioid-treated CLBP.** This RCT also provided data for the estimates of effect sizes and sample size, advanced the conceptual model, supported the role of pain coping as a 'mechanism of change' and suggested dose-response phenomenon. It also supported our hypothesis that the between-group differences found in pain and function will eventually translate to decreased opioid use.

DEFINITION OF AN ADAPTIVE TREATMENT STRATEGY

ATSs are also known as: **treatment algorithms, stepped care interventions, dynamic treatment regimes,** discontinuation (DeMets) **or augmentation strategies, structured treatment interruptions, tailored interventions, …**

An adaptive treatment strategy (ATS) is **a sequence of** ***individually*** **tailored decision rules** that specify whether, how, and when to alter the intensity, type, dosage, or delivery of treatment at critical decision points in the medical care process.

ATSs operationalize sequential decision making with **the aim of improving clinical practice**, in a sense ATS mimics clinical practice.

WHY ADAPTIVE TREATMENT STRATEGIES?

Can be used to inform how to best…

- Adapt treatment to a subject's chronic/changing course
- Deliver appropriate treatment when needed most
- React to non-adherence or side-effect profiles
- Reduce treatment burden on the subject
- Deliver early treatments with positive downstream effects
- Have ability to sift through available treatment options
- More personalized care, over time
- Improving clinical practice

WHEN TO USE ADAPTIVE TREATMENT STRATEGIES?

Use if you expect that there will be significant variation in treatment effects across subjects in comparisons of fixed treatments.

GOAL OF ADAPTIVE TREATMENT STRATEGIES

Maximize strength of treatment

By well chosen moderators, well measured moderators, & well conceived dosage assignment rules

Maximize replicability in the future

Fidelity and implementation and by clearly defining the treatment

DEVELOPING AN ATS REQUIRES CAREFUL CONSIDERATION

- For who are we developing the adaptive strategy? **Population, or Context, question.**
- What is the goal of the adaptive treatment strategy? **Objectives question.**
- What is the optimal sequencing of treatments? **Sequencing question.**
- When do we switch, augment, or maintain treatment? **Timing question.**
- Based on what information do we make decisions? **Tailoring question.**

TAILORING VARIABLES AND DECISION ALGORITHMS

- Tailoring variables: subjects characteristics and intermediate outcomes (e.g., response or adherence to past treatment).
- Link subjects' values on the tailoring variables with specific levels and types of intervention components
- Example (intervention for improving perceived social support):

First stage intervention = {social skill}
IF evaluation = {non-response}
THEN at Step t+1 apply decision {intensify first stage intervention}
ELSE IF evaluation = {response}
THEN at Step t+1 continue on present intervention

SOME CRITICAL QUESTIONS IN ATS DEVELOPMENT

- What is the best sequencing of treatments?
- What is the best timings of alternations in treatments?
- What information do we use to make these decisions?

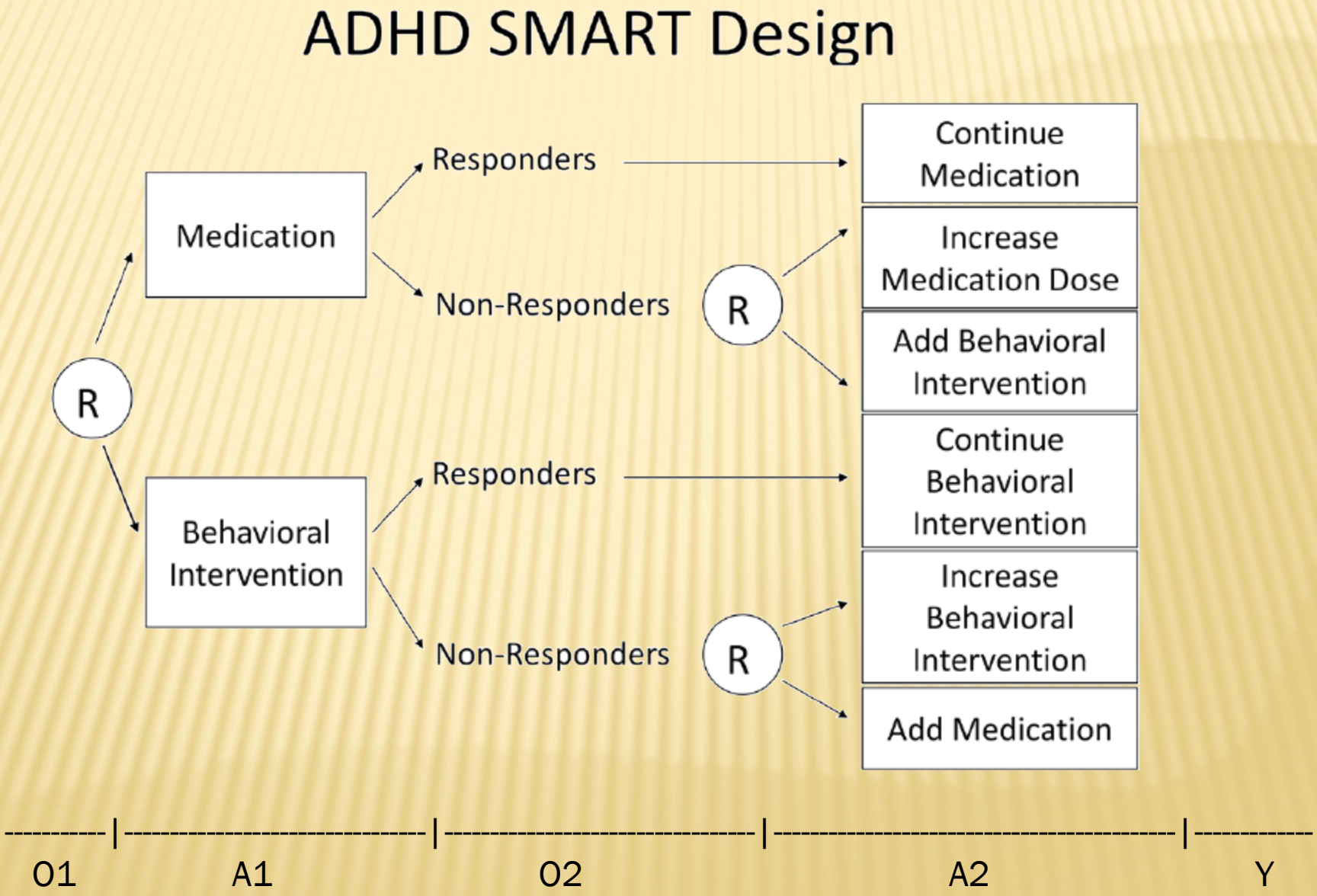
The purpose of **SMART** designs is to provide high quality data for addressing these questions.

WHAT ARE SMART STUDIES?

SMART studies = sequential multiple assignment randomized trial

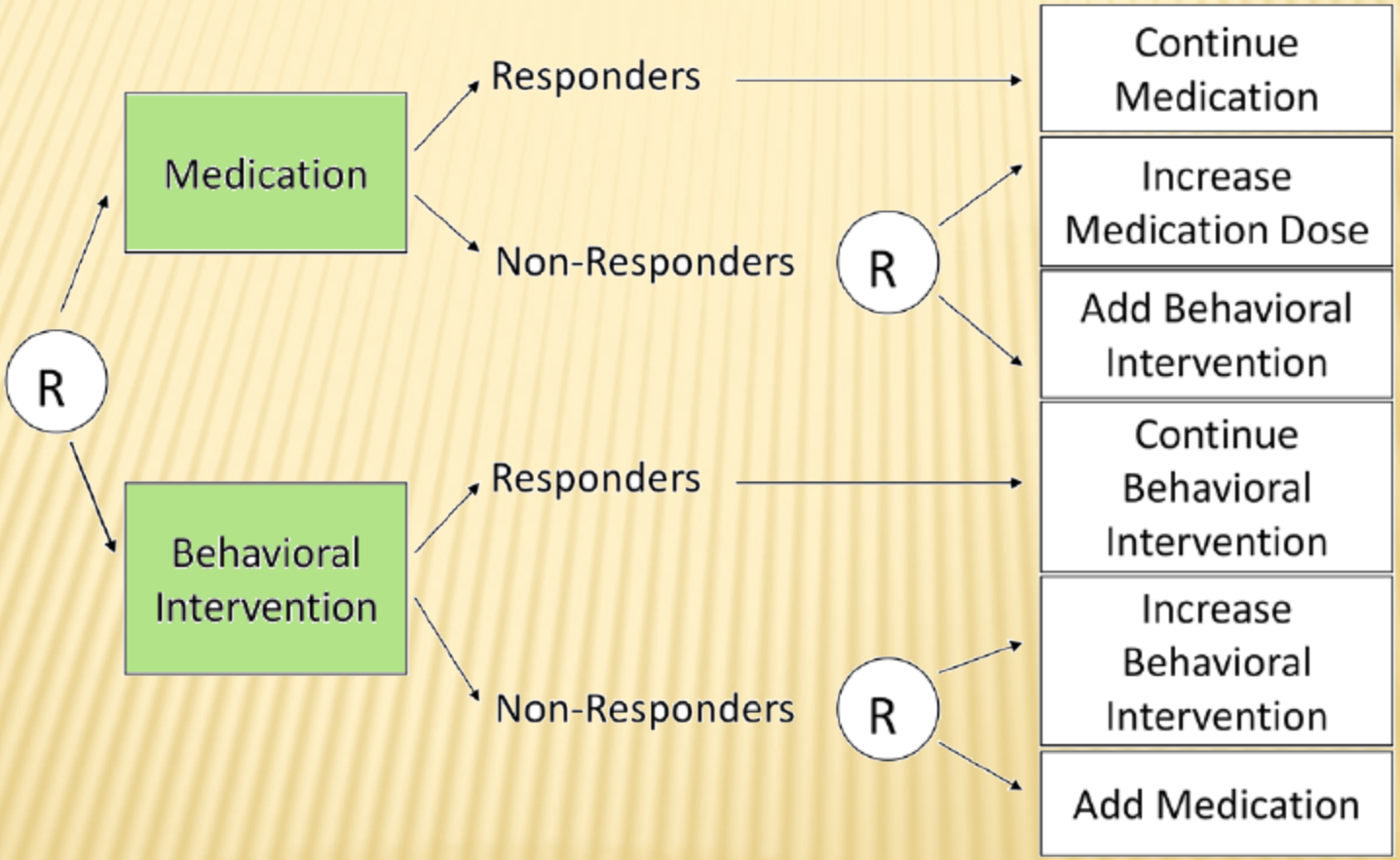
These are multi-stage trials; each stage corresponding to a critical treatment decision with a new randomization taking place at each critical decision, with the goal to inform the construction of adaptive treatment strategies.

Using example of simulated data on ADHA project by (Almirall and Murphy)



There are two “stage 1” treatments

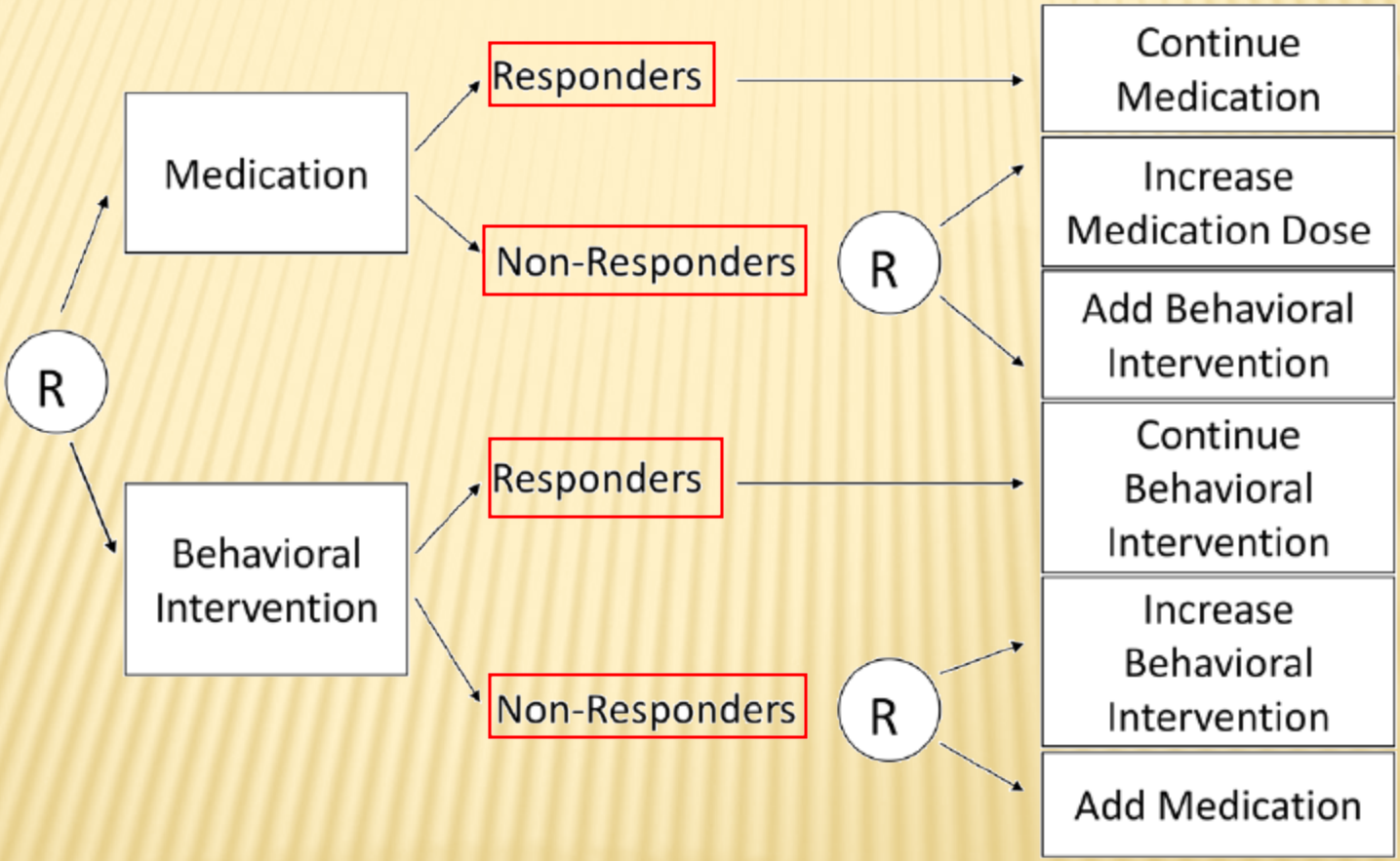
ADHD SMART Design



O1 A1 O2 A2 Y

Tailoring variables – response/non-response

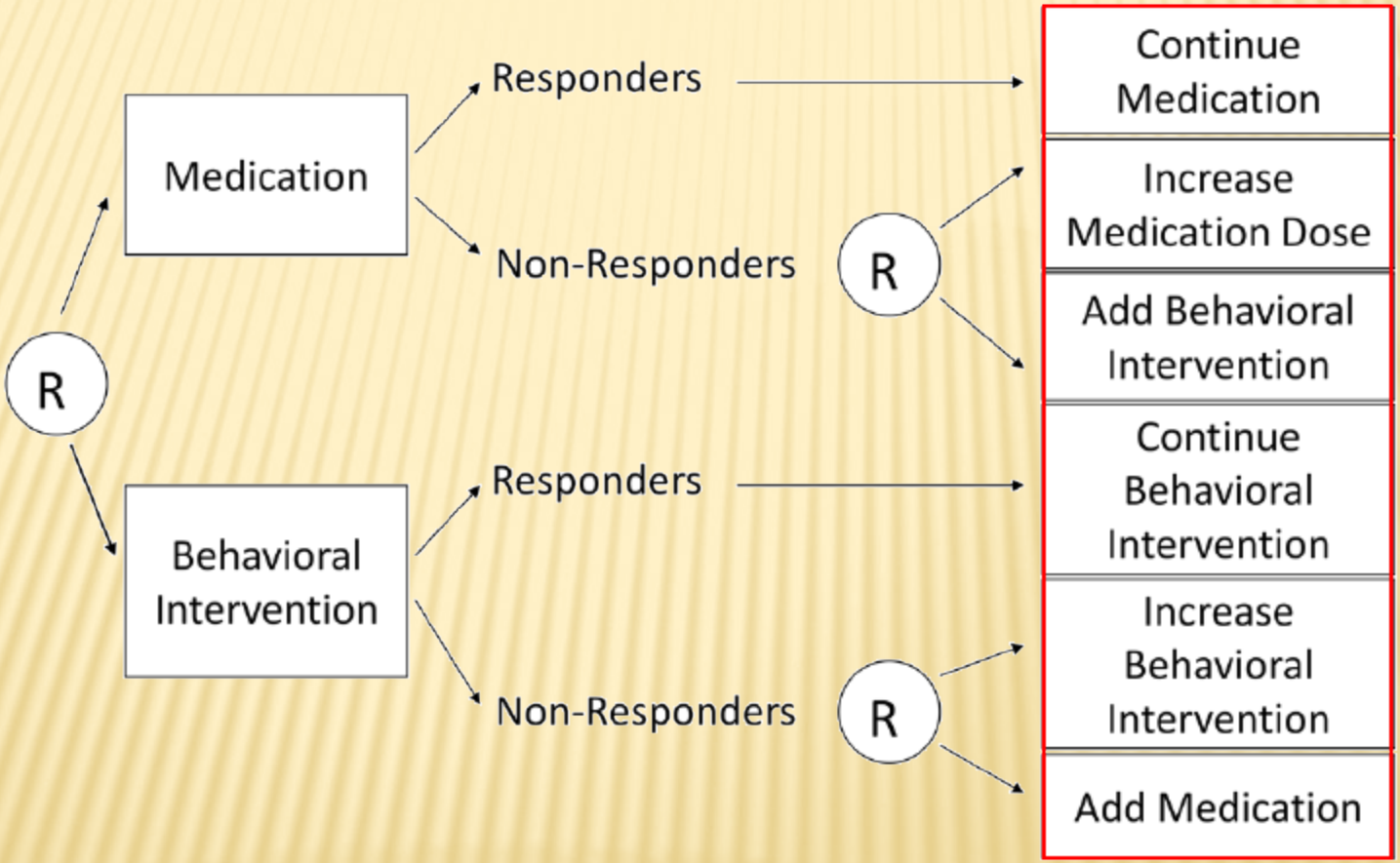
ADHD SMART Design



O1 A1 O2 A2 Y

There are 6 “stage 2” treatments

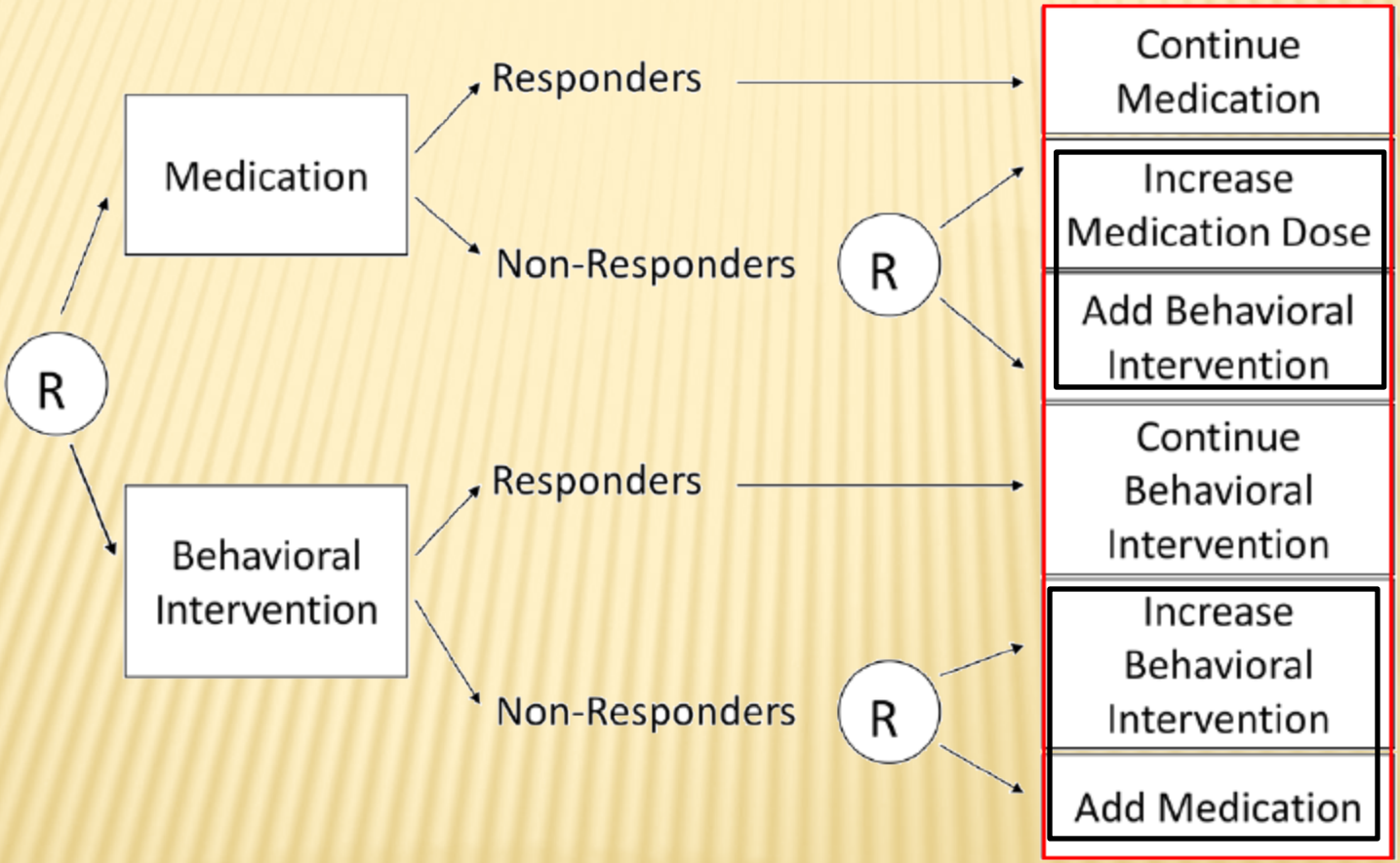
ADHD SMART Design



O1 A1 O2 A2 Y

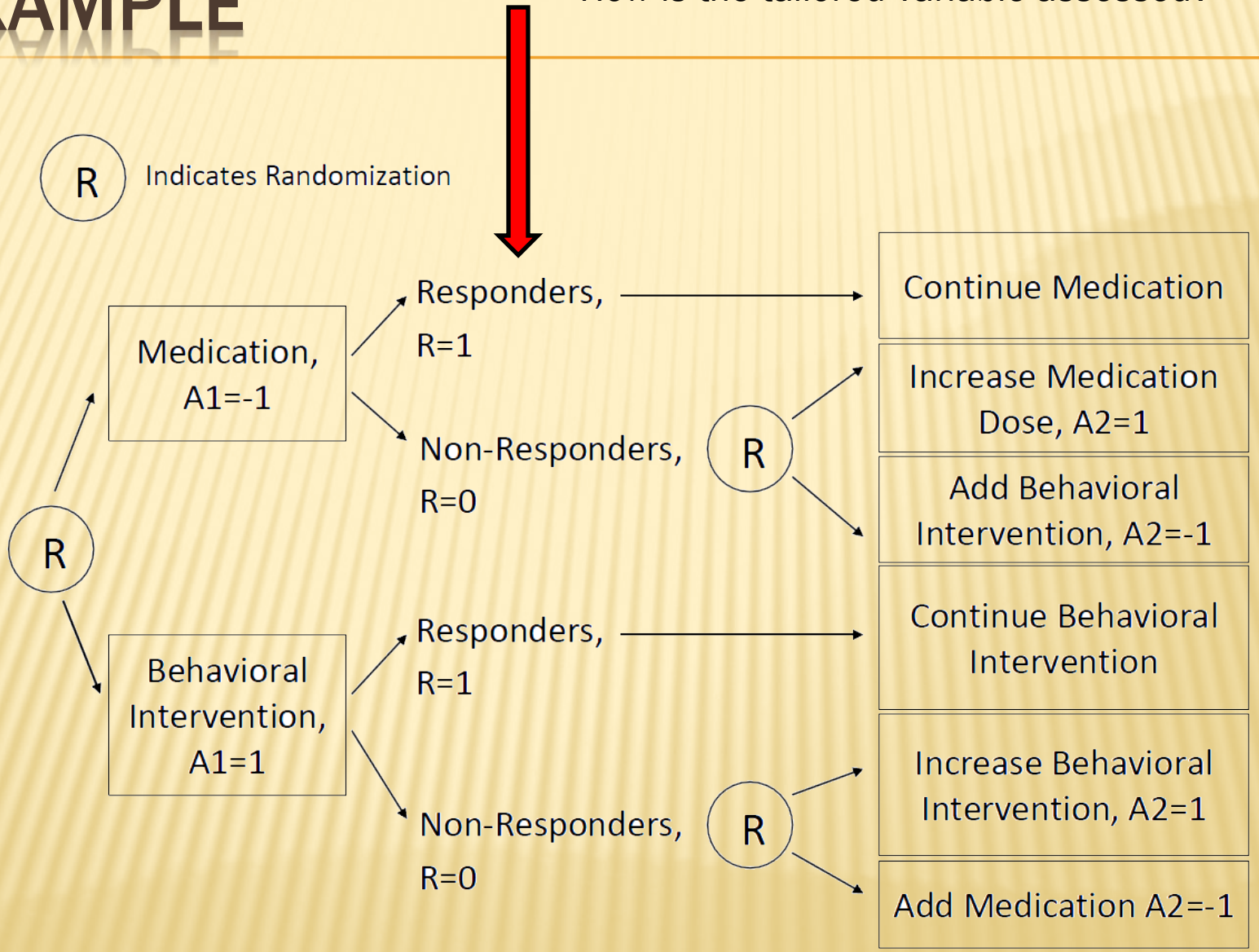
There are 2 “stage 2” treatments assessed for non-responders

ADHD SMART Design



EXAMPLE

How is the tailored variable assessed?



ANALYSIS APPROACH FOR TAILORED VARIABLES

Open for creativity

One possible approach – individual Area Under the Curve (AUC) assessment – (Brown)

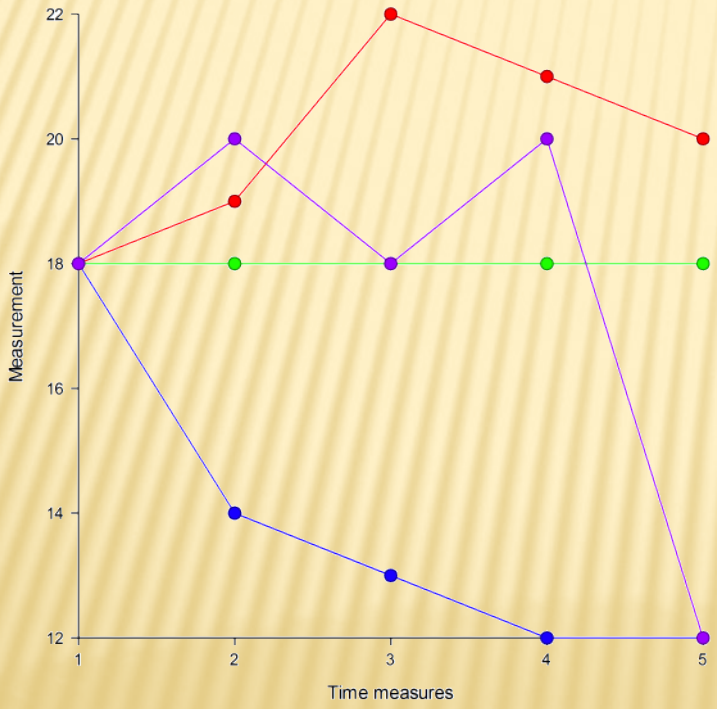
$$AUC = \frac{1}{2}\sum_{i=1}^{n-1}\left(T_{i+1} - T_i\right)\left(C_{i+1} + C_i - 2B\right)$$

Where T_i is the i^{th} time value, C_i is the i^{th} measure, n is the number of time values, and B is the baseline value.

SEQUENTIAL AUC ASSESSMENT OF TAILORED VARIABLES

Area Section with Baseline = 18

C1	Area Under Curve	C3 Max	C2 at Max of Y	C2 Min	C2 Max	Count
1	9	22	3	1	5	5
2	-18	18	1	1	5	5
3	0	18	5	1	5	5
4	1	20	2	1	5	5



AUC Algorithm for depression

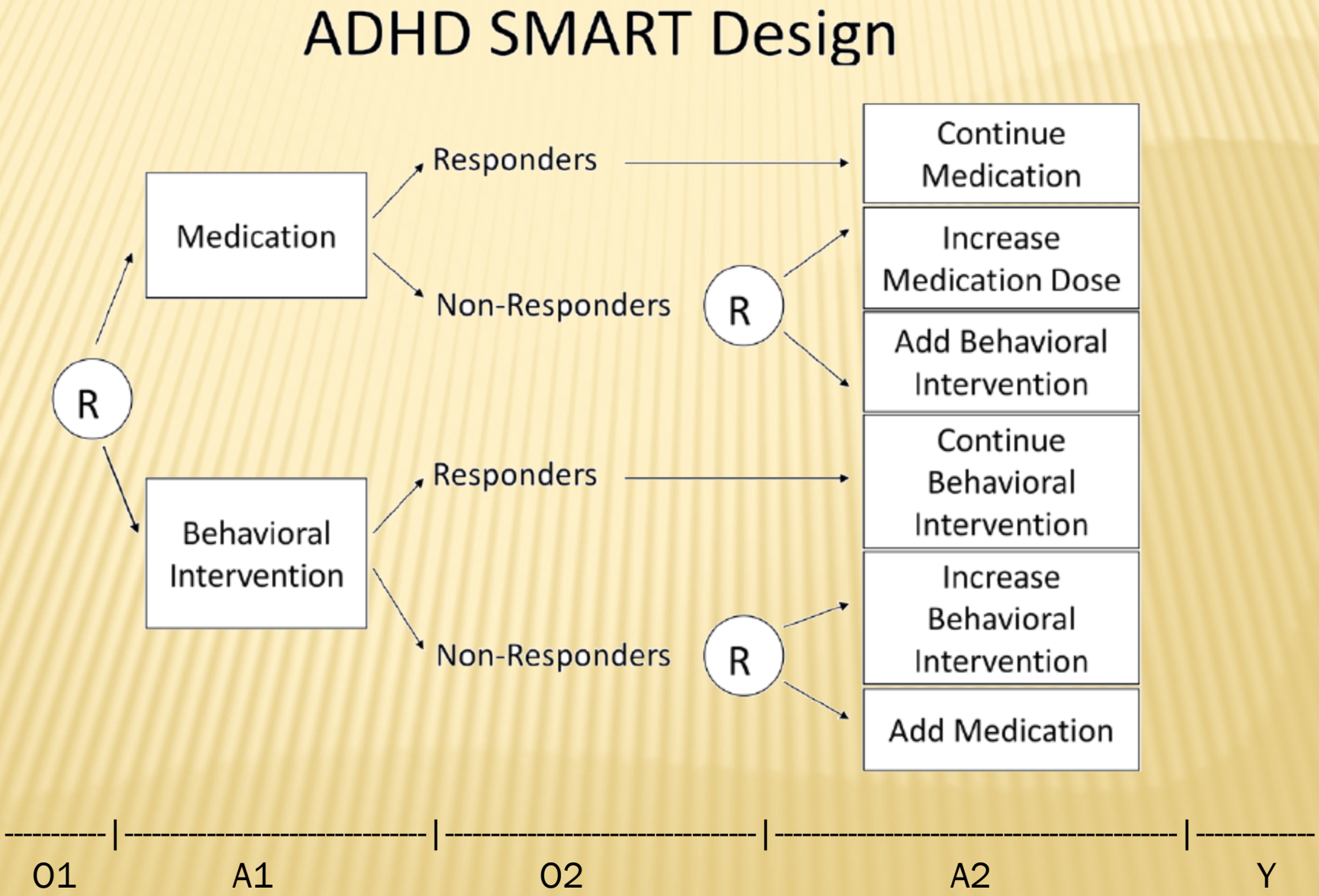
First stage intervention = {CESD}
IF AUC >= Stable AUC (0)
THEN at Step t + 1 {intensify first stage intervention} OR {add other intervention}
ELSE IF AUC < Stable AUC (0)
THEN at Step t + 1 {continue present intervention}

OVERALL ANALYSIS OF THE SMART TRIAL

NOTE: Usually these studies are based on longitudinal data, but to keep things manageable, we will just look at single time point analysis.

- Simple regression based approach
- Q-learning regression approach

Using example of simulated data on ADHA project by Almirall and Murphy



SIMULATED DATA

Variables

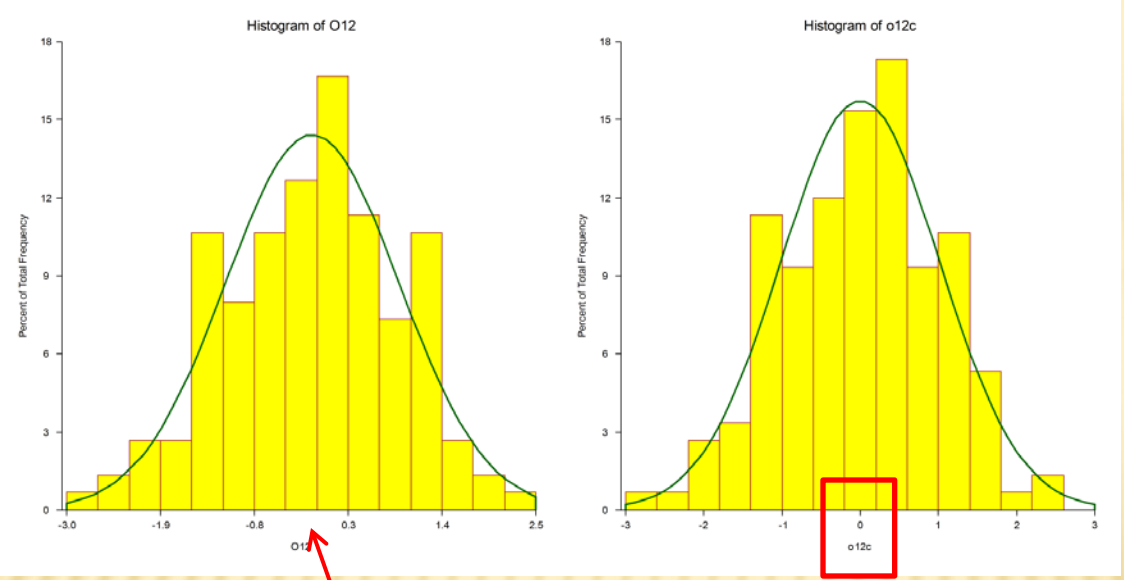
a1 = "initial txt: A1=-1=MED; A1=1=BMOD"
a2 = "second txt: A2=-1=ADD; A2=1=INTSFY"
r = "R=0=early non-response; R=1=early response"
o11 = "oppositional defiant disorder dx at baseline: 1=yes; 0=no"
o12 = "ADHD score at baseline: hi is better"
o13 = "received med prior to txt and found acceptable: 1=yes; 0=no"
o14 = "race: 1=white; 0=non-white"
o21 = "number of months until non-response: missing for responders"
o22 = "adherence to stage 1 intervention: 1=yes; 0=no"
y = "school performance at end of school year"

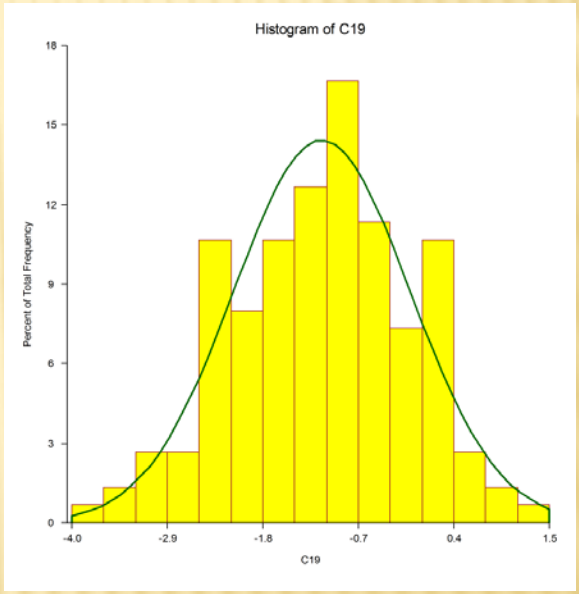
TECHNICAL DETOUR - CENTERING DATA

1. Centering offers a convenient means of achieving readily interpretable parameter estimates.
2. Centering offers better numerical stability during estimation.
3. Centering will not affect the statistical inference.

We can also center dichotomous variables (0,1) without any impact on parameter estimation, other than intercept.

CENTERING





Raw Data

Grand mean centered

Constant deviation (1)

Summary Section of O12

Count	Mean	Standard Deviation	Standard Error	Minimum	Maximum	Range
150	-0.1205948	1.014178	0.08280729	-2.859485	2.439695	5.29918

Don’t believe me?

Skewness and Kurtosis Section of O12

Coefficient Parameter of Dispersion	Skewness	Kurtosis
Value	-0.1129977	2.582127
Std Error	0.1574775	0.2415586

Skewness and Kurtosis Section of o12c

Coefficient Parameter of Dispersion	Skewness	Kurtosis
Value	-0.1129977	2.582127
Std Error	0.1574775	0.2415586

Skewness and Kurtosis Section of C19

Coefficient Parameter of Dispersion	Skewness	Kurtosis
Value	-0.1129977	2.582127
Std Error	0.1574775	0.2415586

CENTERING

Interpretation

Regression Coefficients T-Tests

Independent Variable	Regression Coefficient b(i)	Standard Error Sb(i)	Standardized Coefficient	T-Statistic to Test H0: β(i)=0	Prob Level	Reject H0 at 5%?	Power of Test at 5%
Intercept	2.953286	0.09645262	0.0000	30.619	0.0000	Yes	1.0000
o12c	-0.4988935	0.09542283	-0.3948	-5.228	0.0000	Yes	0.9994

Average effect of o12 on Y. Since this is an average effect we may zero it from the model just leaving the intercept, which is Y for the average o12 value.

So we can say that the outcome (Y) for the average value of o12 is 2.95

$$Y = \beta_0 + \beta_1 X_1 + e_i \quad = \quad Y = \beta_0 + e_i$$

CENTERING

Frequency Distribution of O11

O11	Count	Cumulative Count	Percent	Cumulative Percent	Graph of Percent
0	97	97	64.67%	64.67%	||||||||||||||||||||||||||
1	53	150	35.33%	100.00%	||||||||||||||

Count	Mean	Standard Deviation	Standard Error	Minimum	Maximum	Range
150	0.3533333	0.4796065	0.0391597	0	1	1

Summary Section of Y when O11=0

Count	Mean	Standard Deviation	Standard Error	Minimum	Maximum	Range
97	3.061856	1.329273	0.1349673	1	5	4

Summary Section of Y when O11=1

Count	Mean	Standard Deviation	Standard Error	Minimum	Maximum	Range
53	2.754717	1.175154	0.1614198	1	5	4

Independent Variable	Regression Coefficient b(i)	Standard Error Sb(i)	Standard-ized Coefficient	T-Statistic to Test H0: β(i)=0	Prob Level	Reject H0 at 5%?	Power of Test at 5%
Intercept	3.061856	0.1296845	0.0000	23.610	0.0000	Yes	1.0000
O11	-0.3071387	0.2181704	-0.1150	-1.408	0.1613	No	0.2877
	2.754717						

CENTERING DATA

$$Y = \beta_0 + \beta_1 A_1 + \sum_{k=1}^{K} \cancel{\beta_k} x_k + e_i$$

Grand mean centering dichotomous variables

Frequency Distribution of O11

O11	Count	Cumulative Count	Percent	Cumulative Percent	Graph of Percent
0	97	97	64.67%	64.67%	||||||||||||||||||||||||||
1	53	150	35.33%	100.00%	||||||||||||||

Frequency Distribution of O13

O13	Count	Cumulative Count	Percent	Cumulative Percent	Graph of Percent
0	103	103	68.67%	68.67%	||||||||||||||||||||||||||||
1	47	150	31.33%	100.00%	|||||||||||||

Frequency Distribution of O14

O14	Count	Cumulative Count	Percent	Cumulative Percent	Graph of Percent
0	29	29	19.33%	19.33%	||||||||
1	121	150	80.67%	100.00%	|||||||||||||||||||||||||||||||||

Regression Coefficients T-Tests

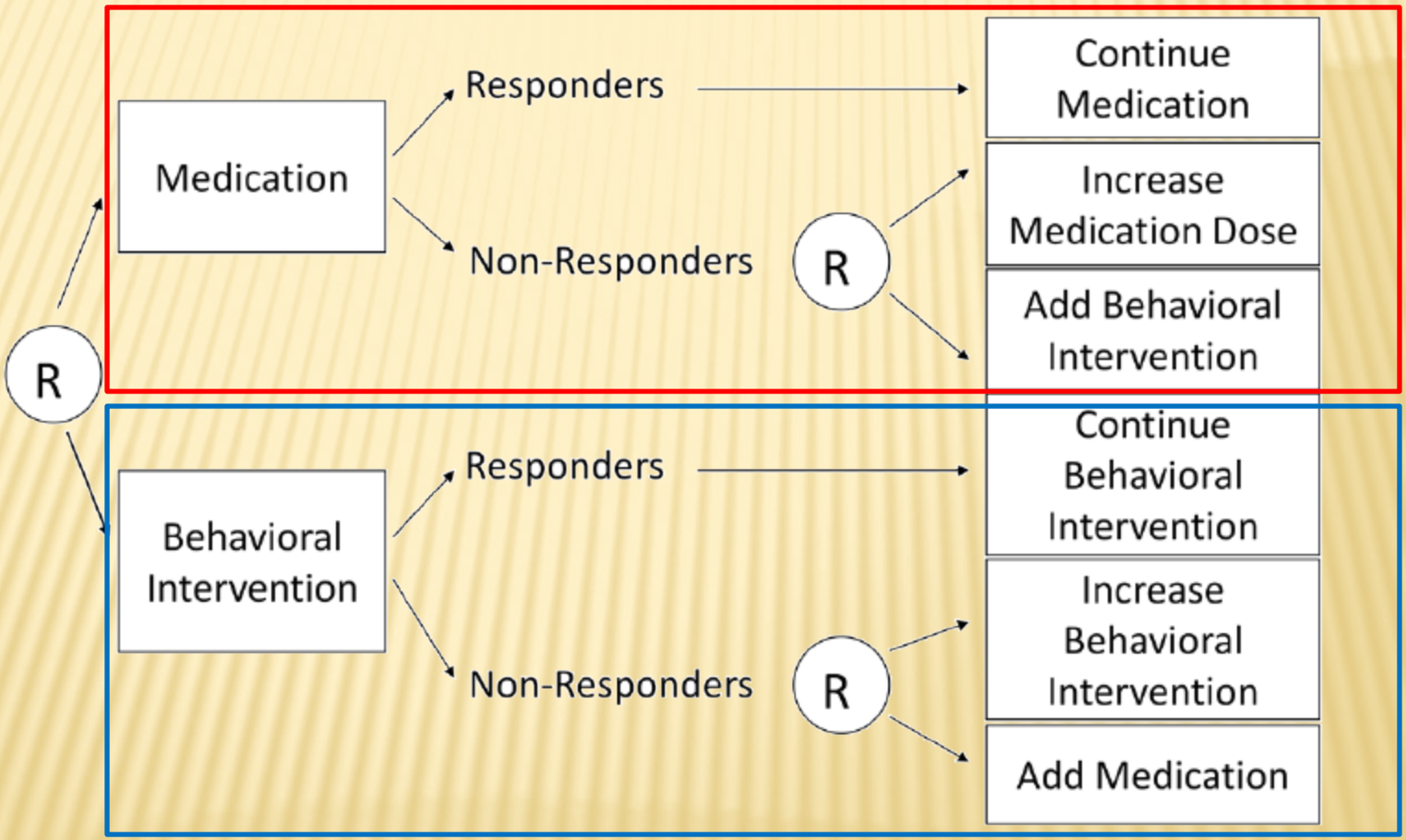
Independent Variable	Regression Coefficient b(i)	Standard Error Sb(i)	Standard-ized Coefficient	T-Statistic to Test H0: β(i)=0	Prob Level	Reject H0 at 5%?	Power of Test at 5%
Intercept	2.455766	0.2571365	0.0000	9.550	0.0000	Yes	1.0000
(A1=1)	0.1850798	0.1926845	0.0725	0.961	0.3384	No	0.1590
O11	-0.2750856	0.2005491	-0.1030	-1.372	0.1723	No	0.2756
O12	-0.4896806	0.09540292	-0.3875	-5.133	0.0000	Yes	0.9992
O13	0.05207713	0.2104568	0.0189	0.247	0.8049	No	0.0569
O14	0.5291572	0.2414031	0.1636	2.192	0.0300	Yes	0.5861

Regression Coefficients T-Tests

Independent Variable	Regression Coefficient b(i)	Standard Error Sb(i)	Standard-ized Coefficient	T-Statistic to Test H0: β(i)=0	Prob Level	Reject H0 at 5%?	Power of Test at 5%
Intercept	2.860721	0.1353815	0.0000	21.131	0.0000	Yes	1.0000
(A1=1)	0.1850798	0.1926845	0.0725	0.961	0.3384	No	0.1590
o11c	-0.2750856	0.2005491	-0.1030	-1.372	0.1723	No	0.2756
o12c	-0.4896806	0.09540292	-0.3875	-5.133	0.0000	Yes	0.9992
o13c	0.05207713	0.2104568	0.0189	0.247	0.8049	No	0.0569
o14c	0.5291572	0.2414031	0.1636	2.192	0.0300	Yes	0.5861

Primary Question is simple two group comparison

ADHD SMART Design



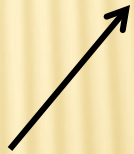
WE WILL USE GLM TO ASSESS QUESTION 1

$$Y = \beta_0 + \beta_1 a_1 + \beta_2 o_{11c} + \beta_2 o_{12c} + \beta_2 o_{13c} + \beta_2 o_{14c}$$

a1 = "initial txt: A1=-1=MED; A1=1=BMOD"
a2 = "second txt: A2=-1=ADD; A2=1=INTSFY"
r = "R=0=early non-response; R=1=early response"
o11 = "oppositional defiant disorder dx at baseline: 1=yes; 0=no"
o12 = "ADHD score at baseline: hi is better"
o13 = "received med prior to txt and found acceptable: 1=yes; 0=no"
o14 = "race: 1=white; 0=non-white"
o21 = "number of months until non-response: missing for responders"
o22 = "adherence to stage 1 intervention: 1=yes; 0=no"
y = "school performance at end of school year"

USING SAS PROC GENMOD

```
proc genmod data = one;
      model y = a1 o11c o12c o13c o14c;
      estimate 'Mean Y under BMOD' intercept 1 a1 1 o11c 0 o12c 0 o13c 0 o14c 0;
      estimate 'Mean Y under MED'  intercept 1 a1 -1 o11c 0 o12c 0 o13c 0 o14c 0;
      estimate 'Between groups diff          ' a1 2 o11c 0 o12c 0 o13c 0 o14c 0;
run;
```



Centered variables zero'd

RESULTS – QUESTION 1

Analysis Of Maximum Likelihood Parameter Estimates

Parameter	DF	Estimate	Standard Error	Wald 95% Confidence Limits		Wald Chi-Square	Pr > ChiSq
Intercept	1	2.9533	0.0932	2.7706	3.1359	1004.29	<.0001
A1	1	0.0925	0.0944	-0.0925	0.2776	0.96	0.3269
o11c	1	-0.2751	0.1965	-0.6602	0.1100	1.96	0.1615
o12c	1	-0.4897	0.0935	-0.6729	-0.3065	27.44	<.0001
o13c	1	0.0521	0.2062	-0.3521	0.4562	0.06	0.8006
o14c	1	0.5292	0.2365	0.0656	0.9927	5.01	0.0253
Scale	1	1.1413	0.0659	1.0192	1.2781		

Contrast Estimate Results

Label	Mean Estimate	Mean Confidence Limits		L'Beta Estimate	Standard Error	Alpha
Mean Y under BMOD	3.0458	2.7858	3.3058	3.0458	0.1326	0.05
Mean Y under MED	2.8607	2.6007	3.1207	2.8607	0.1326	0.05
Between groups diff	0.1851	-0.1849	0.5551	0.1851	0.1888	0.05

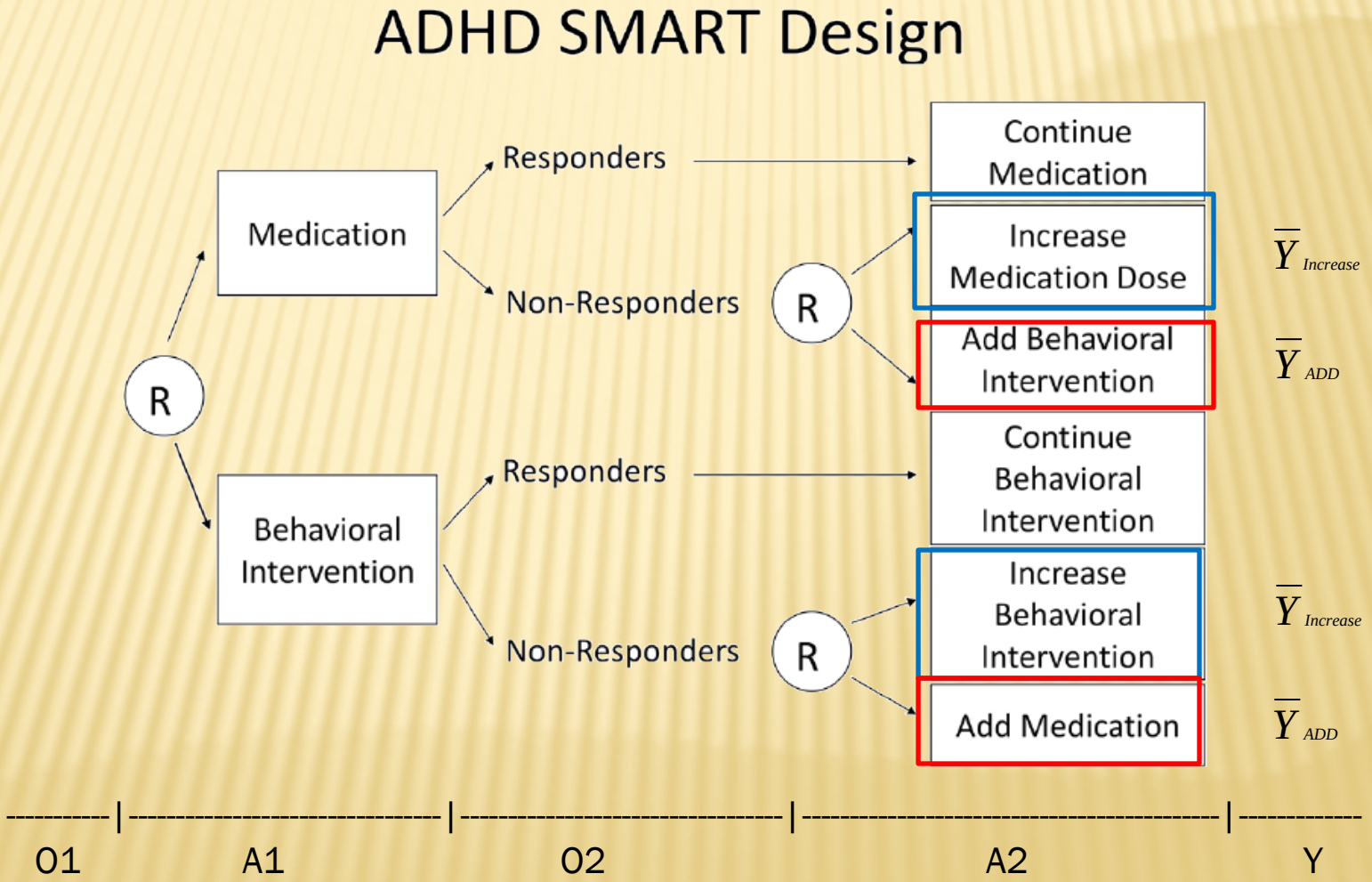
Contrast Estimate Results

Label	L'Beta Confidence Limits		Chi-Square	Pr > ChiSq
Mean Y under BMOD	2.7858	3.3058	527.25	<.0001
Mean Y under MED	2.6007	3.1207	465.12	<.0001
Between groups diff	-0.1849	0.5551	0.96	0.3269

Overall, the BMOD treatment is better than the MED treatment, but not statistically significant (p = 0.3269)

QUESTION 2 – WHAT IS THE BEST SECOND-STAGE TREATMENT TACTIC?

Of the children who do not respond to either of the first stage treatments, is it better to enhance/increase the treatment or add a different treatment?



SUB-SET R=0 FOR NON-RESPONDERS

```
data two;set one;
 if r = 0;
proc genmod data = two;
     model y = a2     o11c o12c o13c o14c o21c o22c;
     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;
```

Non-responsive

Centered variables zero'd – blank is the same as zero.

```
a1 = "initial txt: A1=-1=MED; A1=1=BMOD"
a2 = "second txt: A2=-1=ADD; A2=1=INTSFY"
r = "R=0=early non-response; R=1=early response"
o11 = "oppositional defiant disorder dx at baseline: 1=yes; 0=no"
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o13 = "received med prior to txt and found acceptable: 1=yes; 0=no"
o14 = "race: 1=white; 0=non-white"
o21 = "number of months until non-response: missing for responders"
o22 = "adherence to stage 1 intervention: 1=yes; 0=no"
y   = "school performance at end of school year"
```

RESULTS

Analysis Of Maximum Likelihood Parameter Estimates

Parameter	DF	Estimate	Standard Error	Wald 95% Confidence Limits		Wald Chi-Square	Pr > ChiSq
Intercept	1	2.9002	0.1078	2.6890	3.1115	724.20	<.0001
A2	1	-0.2939	0.1104	-0.5103	-0.0776	7.09	0.0077
o11c	1	-0.2121	0.2347	-0.6721	0.2480	0.82	0.3663
o12c	1	-0.4914	0.1108	-0.7086	-0.2743	19.67	<.0001
o13c	1	0.1684	0.2441	-0.3101	0.6470	0.48	0.4903
o14c	1	0.4464	0.2818	-0.1058	0.9987	2.51	0.1131
o21c	1	-0.0050	0.0545	-0.1118	0.1018	0.01	0.9272
o22c	1	-0.1702	0.2205	-0.6023	0.2619	0.60	0.4401
Scale	1	1.0667	0.0758	0.9280	1.2262		

Contrast Estimate Results

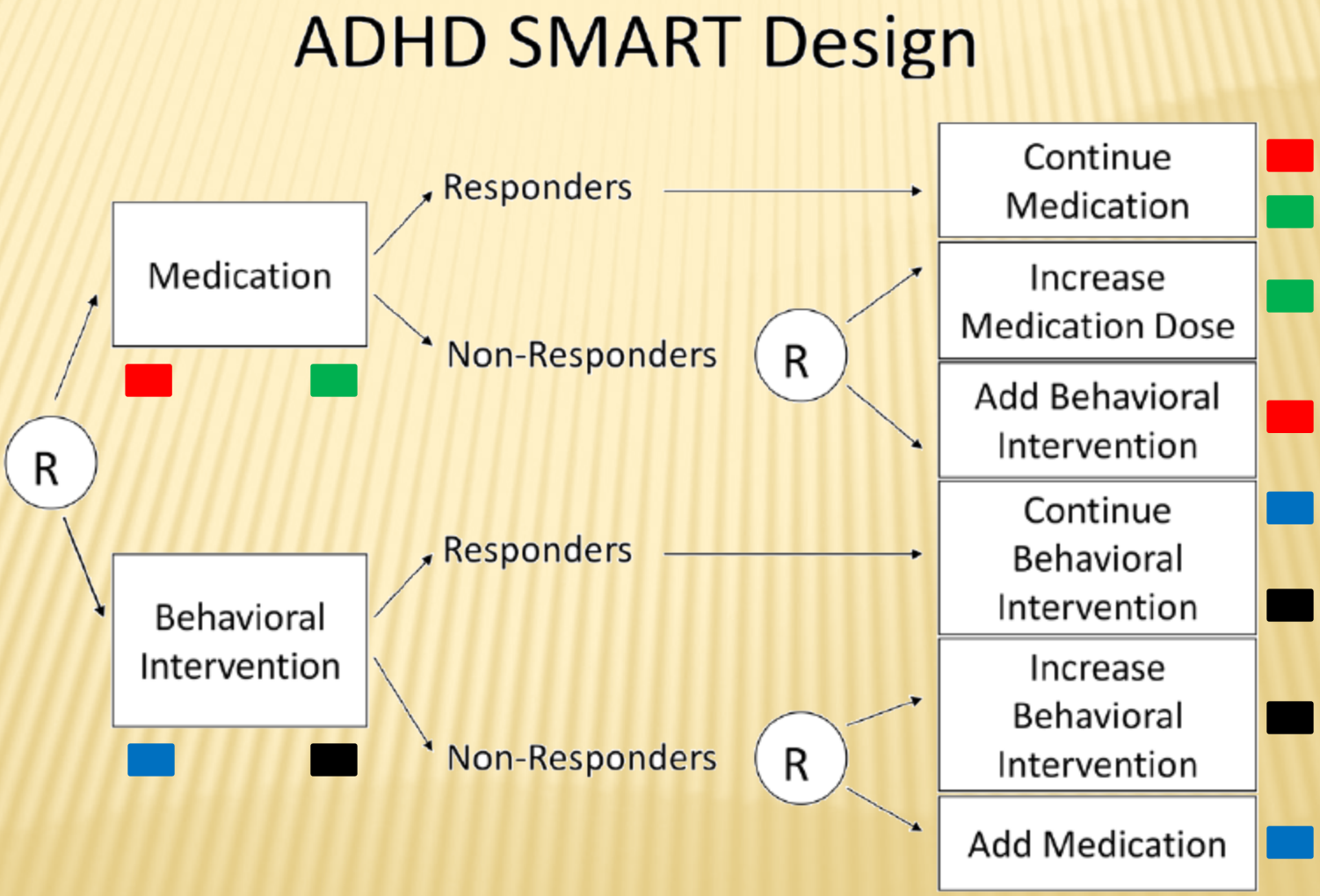
Label	Mean Estimate	Mean Confidence Limits		L'Beta Estimate	Standard Error	Alpha
Mean Y w/INTENSIFY tactic	2.6063	2.3054	2.9071	2.6063	0.1535	0.05
Mean Y w/ADD TXT tactic	3.1942	2.8903	3.4980	3.1942	0.1550	0.05
Between groups difference	-0.5879	-1.0206	-0.1552	-0.5879	0.2208	0.05

Contrast Estimate Results

Label	L'Beta Confidence Limits		Chi-Square	Pr > ChiSq
Mean Y w/INTENSIFY tactic	2.3054	2.9071	288.31	<.0001
Mean Y w/ADD TXT tactic	2.8903	3.4980	424.42	<.0001
Between groups difference	-1.0206	-0.1552	7.09	0.0077

On average, the tactic of ADDING is better and it is statistically significant, p=0.0077.

THERE ARE 4 ATS'S IN THIS SMART



TESTING THE ATS

We may then proceed by testing the various ATS's, for example:

ATS Red:

First treat with medication, then

- ❑ if responds, continue with medication treatment
- ❑ if doesn't respond, then ADD BMOD treatment

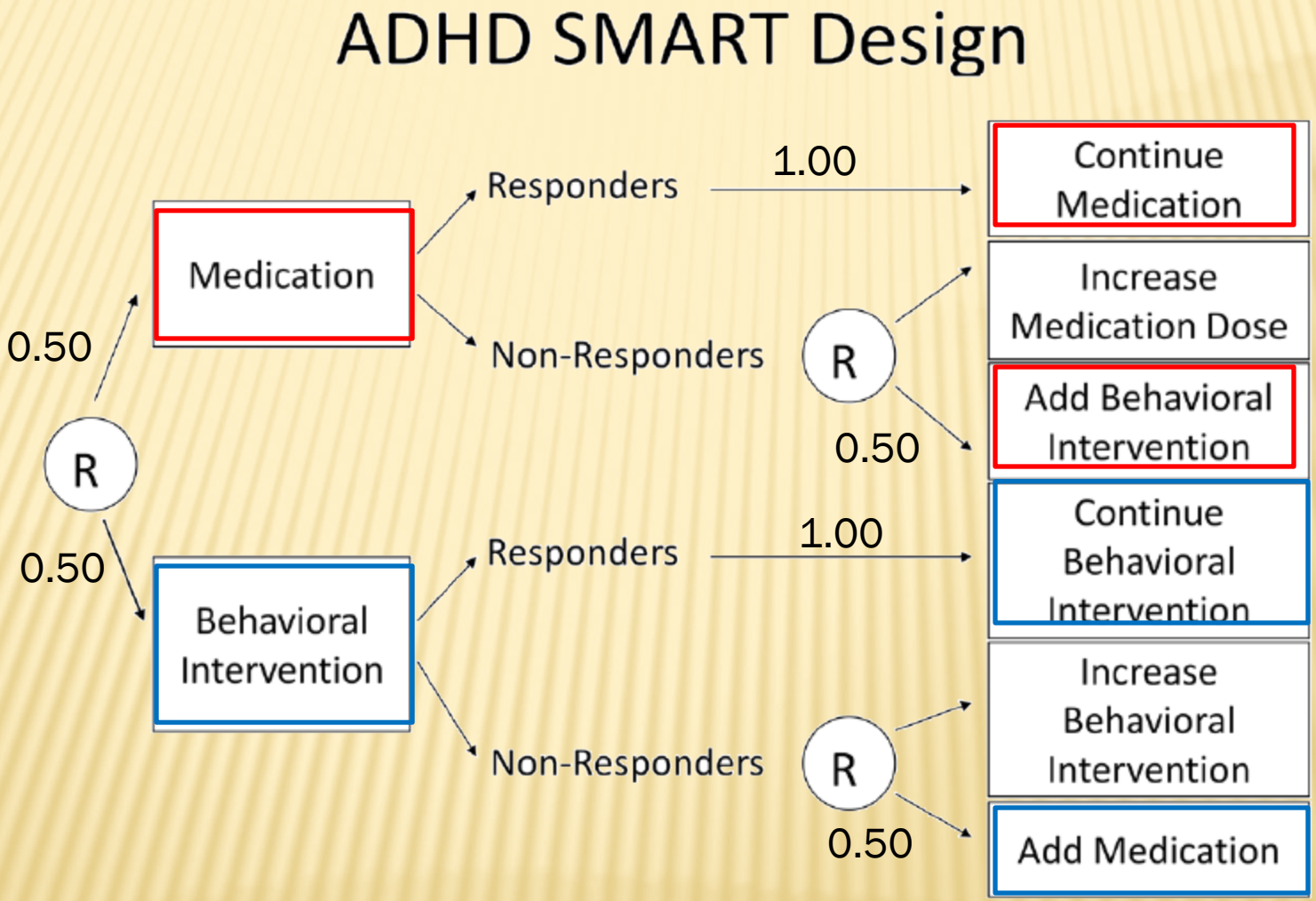
Versus

ATS Blue:

First treat with BMOD, then

- ❑ if responds, continue with BMOD treatment
- ❑ if doesn't respond, then ADD mediation treatment

Contrasting ATS's (Red versus Blue)



Responders have 0.5 chance of continuing in the ATS
Non-responders have a 0.25 chance of continuing in the ATS (0.5 x 0.5 = 0.25), so responders are over-represented in this design.

RESULTS OF RED AND BLUE ATS

Parameter	Estimate	Standard Error	95% Confidence Limits		Z	Pr > |Z|
Intercept	3.2787	0.1115	3.0602	3.4971	29.41	<.0001
Z1	-0.2558	0.0984	-0.4486	-0.0629	-2.60	0.0093
o11c	-0.0158	0.2201	-0.4471	0.4155	-0.07	0.9427
o12c	-0.3562	0.0993	-0.5508	-0.1617	-3.59	0.0003
o13c	-0.2718	0.2816	-0.8238	0.2801	-0.97	0.3344
o14c	0.1826	0.3210	-0.4465	0.8118	0.57	0.5694
o21c	-0.0128	0.0571	-0.1247	0.0992	-0.22	0.8228
o22c	-1.2947	0.2369	-1.7591	-0.8303	-5.46	<.0001

Contrast Estimate Results

Label	Mean Estimate	Mean Confidence Limits		L'Beta Estimate	Standard Error	Alpha
Mean Y under red ATS	3.0229	2.6918	3.3539	3.0229	0.1689	0.05
Mean Y under blue ATS	3.5344	3.2889	3.7799	3.5344	0.1253	0.05
Diff: red - blue	-0.5115	-0.8973	-0.1258	-0.5115	0.1968	0.05

Contrast Estimate Results

Label	L'Beta Confidence Limits		Chi-Square	Pr > ChiSq
Mean Y under red ATS	2.6918	3.3539	320.27	<.0001
Mean Y under blue ATS	3.2889	3.7799	796.25	<.0001
Diff: red - blue	-0.8973	-0.1258	6.76	0.0093

Following the blue ATS leads to better performance than following the red, and is statistically significant (p-value = 0.0093), after controlling for various covariates.

TESTING THE ATS

We may then proceed by testing the various ATS's combinations.

Q-LEARNING (WATKINS, 1989; MURPHY, 2005)

- Popular method from computer science.
- Regression-based: one regression for each stage.
- Backwards induction: moving backwards in time from the last stage to the first stage.

ADVANTAGES OF Q-LEARNING APPROACH

- Reduces potential bias resulting from mediators of the relationship between the first stage intervention and the primary outcome.
- Reduces potential bias resulting from unmeasured causes (U) of both the tailoring variables and the primary outcome.
- PROC QLEARN (SAS) will model the Q-learning approach.

WHERE BEST TO USE SMART DESIGN?

- R21 – pilot/feasibility studies
- Small developmental grants

NIH Funding Announcement Calls for Sequential, Multiple Assignment, Randomized Trials (SMARTs)

January 17, 2013

A new announcement from NIH seeks proposals that improve behavioral treatments for drug abuse, HIV, chronic pain, or related behaviors. PA-13-077 is sponsored by the National Institute on Drug Abuse (NIDA), the National Institute on Alcohol Abuse and Alcoholism (NIAAA), and the Office of Behavioral and Social Sciences Research (OBSSR). This program announcement specifically solicits proposals featuring sequential, multiple assignment, randomized trial (SMART) designs because of SMART's applicability to efficacy studies and to translating interventions into real world settings.

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

OBSSR

NIAAA NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM

CREDIT

These are the real experts

- Susan Murphy – University of Michigan
- Janet Levy – Duke University School of Nursing
- Alena Oetting – University of Michigan
- Roger Weiss – Harvard Medical School
- Linda Collins – Pennsylvania State University

THANK YOU

DISCUSSION