Introduction to a SMART Way to Construct Adaptive Interventions (Using MOST)

Daniel Almirall[1,2] Inbal (Billie) Nahum-Shani[1,2]
Linda M. Collins[2,3,5] Susan A. Murphy[1,2,4]

[1]Institute for Social Research, University of Michigan
[2]The Methodology Center, Penn State University
[3]Human Development and Family Studies, Pennsylvania State University
[4]Department of Statistics, University of Michigan
[5]Department of Statistics, Pennsylvania State University

HIV MP3 Meeting - Washington DC - 11-13-2013

Outline

Adaptive Interventions
- What? Why?

Evaluating versus Building an Adaptive Intervention?
- Multi-phase Optimization STrategy (MOST) Framework

Sequential Multiple Assignment Randomized Trial (SMART)
- What are SMARTs?

SMART Design Principles
- Keep it Simple
- Choosing Primary and Secondary Hypotheses

Take Home Points

Other Example SMARTs

ADAPTIVE INTERVENTIONS

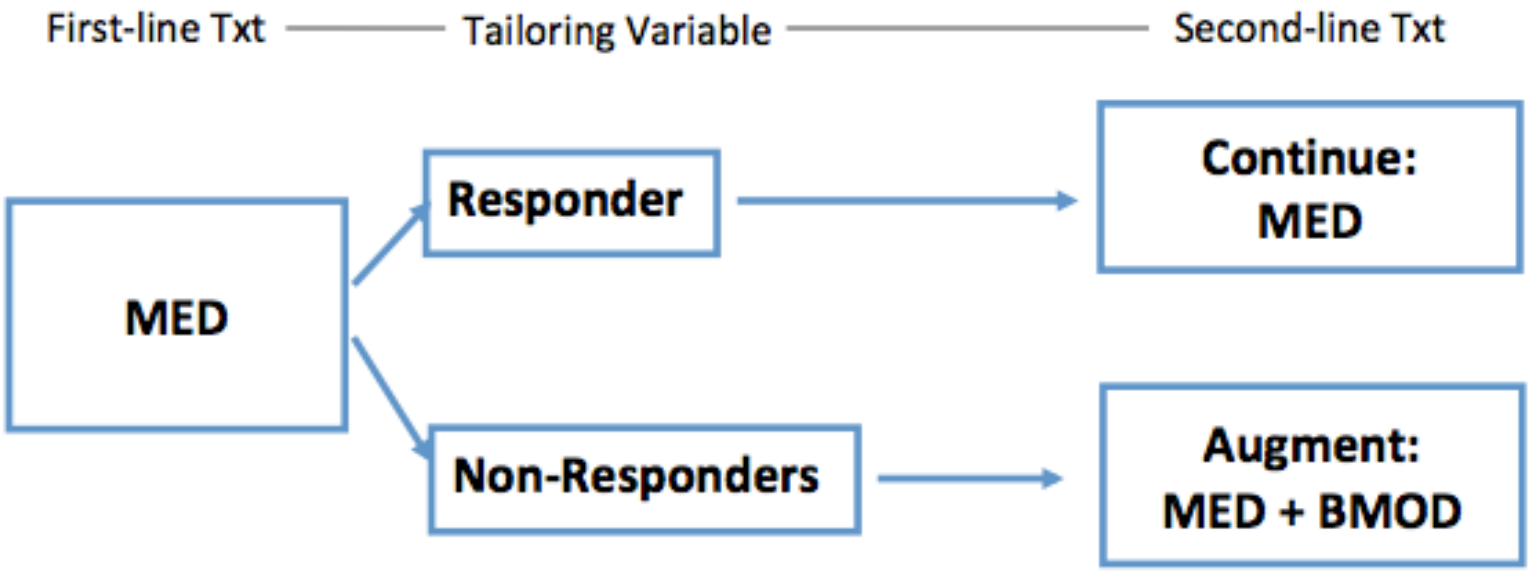
Definition: An Adaptive Intervention is

- a sequence of individually tailored decision rules
- that specify whether, how, and/or when
- to alter the intensity, type, dosage, or delivery of treatment
- at critical decision points in the course of care.

Adaptive Interventions operationalize sequential decision making with **the aim of improving clinical practice**.

Concrete Example of an Adaptive Intervention

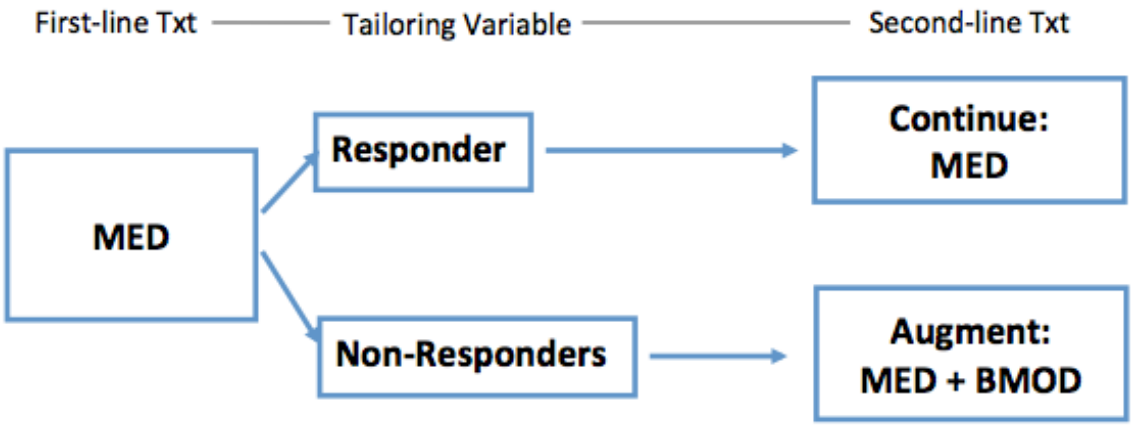
ADHD in Children, Ages 6-12



- Goal is to minimize the child's symptom profile/trajectory.

What makes up an Adaptive Intervention?

1. Critical decisions: treatment options and more
2. Tailoring variables: to decide how to adapt treatment
3. Decision rules: inputs tailoring variable, outputs one or more recommended treatments



Adaptive interventions AKA: dynamic treatment regimes, adaptive treatment strategies, treatment algorithms, structured treatment interruptions in HIV treatment

Why Adaptive Interventions?

Necessary...

- Nature of chronic disorders/phenomena (substance use, mental health, diabetes, cancer, HIV treatment adherence)
  - Waxing and waning course (multiple relapse, recurrence)
  - Life events, co-occuring disorders may arise
- Disorders for which there is no widely effective treatment.
- Disorders for which there are widely effective treatments, but they are costly or burdensome.
- Bottom line: High heterogeneity in response to treatment
  - Within person (over time) and between person

All require sequences of treatment decisions!

SIDEBAR: A NEW FRAMEWORK FOR CONDUCTING INTERVENTIONS RESEARCH: WITH APPLICATION TO ADAPTIVE INTERVENTIONS

The Multiphase Optimization STrategy (MOST)

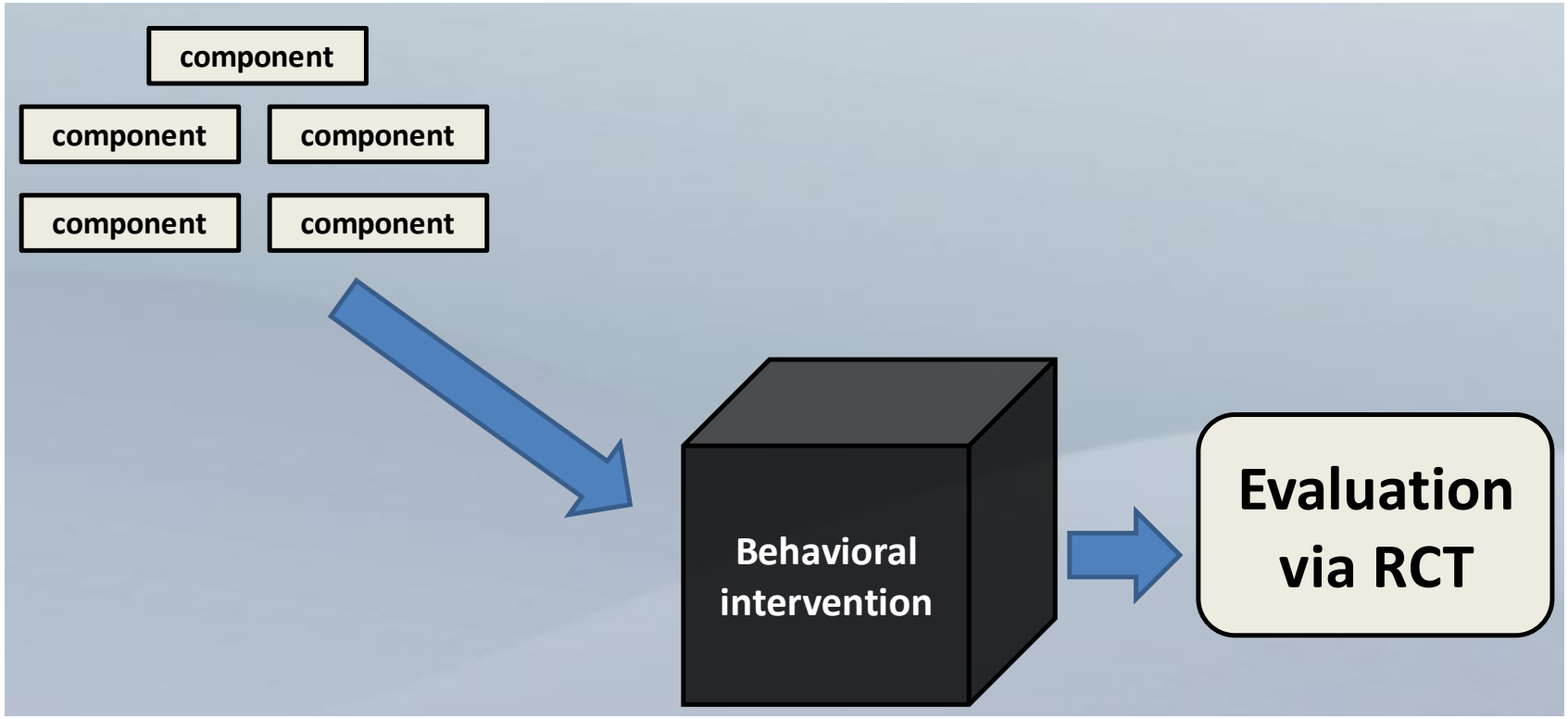
All MOST slides are taken from Linda Collin's talk at HIV Workshop in Oct.

- An engineering-inspired **framework** for development, optimization, and evaluation of behavioral interventions.
- A focus has been on engineering high-quality multi-component interventions. (Adaptive interventions are a type of multi-component intervention.)
- Using MOST it is possible to engineer a behavioral intervention to meet a specific optimization criterion.

Collins, Murphy, Nair, Strecher, 2005; Collins, Murphy, and Strecher, 2007; Collins, Baker, Mermelstein, et al. 2011

Current practice uses the treatment package approach

MOST slides taken/modified from Linda Collin's talk at HIV Methods Workshop in Oct.



So what is wrong with a well-conducted RCT?

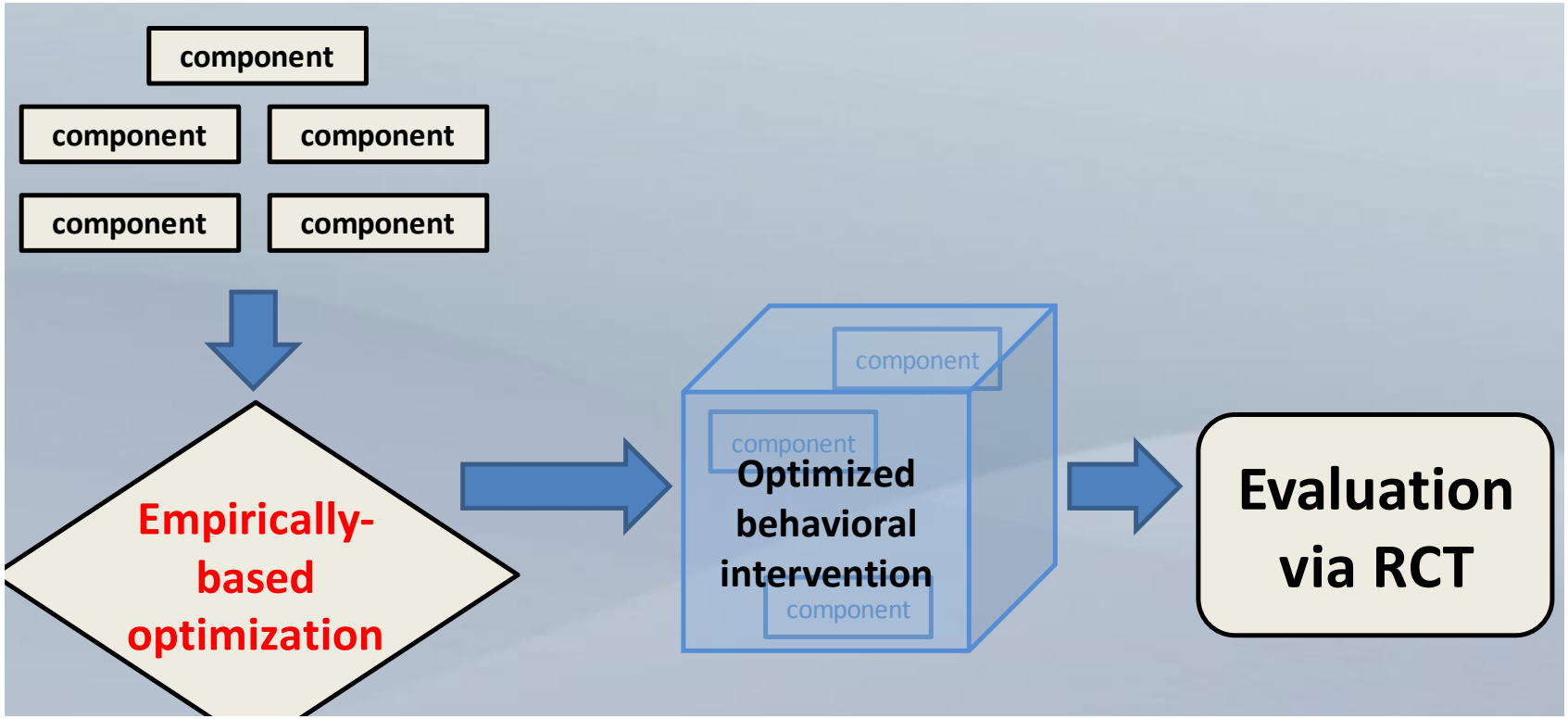
Absolutely Nothing is Wrong with a Well-Conducted RCT!
(We love RCTs of all types!)

But...

- If a clinically significant effect is found, an RCT does not tell you which components were actually active/useful.
- If a clinically significant effect is not found, an RCT does not tell you which components to retain for future study.

MOST is conjectured to be a more principled approach

MOST slides taken/modified from Linda Collin's talk at HIV Methods Workshop in Oct.



MOST has Three Phases

1. Preparation
   - Id candidate components, pilots to examine feasibility/acceptability, theoretical models, expert consensus, observational studies (mathematical modeling)
2. Optimization*
   - Via experimentation: Screen out ineffective components, refine (txt effect heterogeneity), and assemble intervention
   - Ex: Factorial deigns; Fractional factorial designs; SMARTs (which we discuss today, are a special type of factorial design for optimizing an adaptive intervention)
3. Evaluation
   - Confirmation of effectiveness of intervention via RCT

Repeat.*

SO... LET'S GET BACK TO ADAPTIVE INTERVENTIONS AND APPLY THE "MOST THINKING"...

GENERATING HYPOTHESES vs BUILDING vs EVALUATING

ADAPTIVE INTERVENTIONS?

3 Different Research Questions/Aims = 3 Different Research Designs

- **Aim 1**: When **generating hypotheses** about an Adaptive Intervention: e.g., Does augmenting txt (as observed in a previous trial) for non-responders correlate with better outcomes?
- **Aim 2**: When **building** an Adaptive Intervention: e.g, What are the best tailoring variables and/or decision rules?
- **Aim 3**: When **evaluating** a particular Adaptive Intervention: e.g. Does the AI have a (statistically powered) clinically significant effect compared to suitable control?

3 Different Research Questions/Aims = 3 Different Research Designs

Ex. Q1: Does augmenting txt for non-responders (as observed in a previous trial) correlate with better outcomes?

Ex. Q2: What are the best tailoring variables or decision rules?

Ex. Q3: Does the Adaptive Intervention have a statistically and clinically signif. effect as compared to control intervention?

		Observational Studies	Experimental Studies	
Question	Aim	Analysis of Previous RCT	SMART	RCT
1	Hypothesis Gen.	**YES**	$\approx$	$\sim$
2	Building	$\approx$	**YES**	$\approx$
3	Evaluating	$\sim$	$\approx$	**YES**

SEQUENTIAL MULTIPLE ASSIGNMENT RANDOMIZED TRIALS (SMARTs)

What is a Sequential Multiple Assignment Randomized Trial (SMART)?

- Multi-stage trials; same participants throughout
- Each stage corresponds to a critical decision point
- At each stage, subjects randomized to set of treatment options
- **The goal of a SMART is to inform the development of adaptive interventions.**

I will give you an example SMART, but first...

Background for an Example SMART

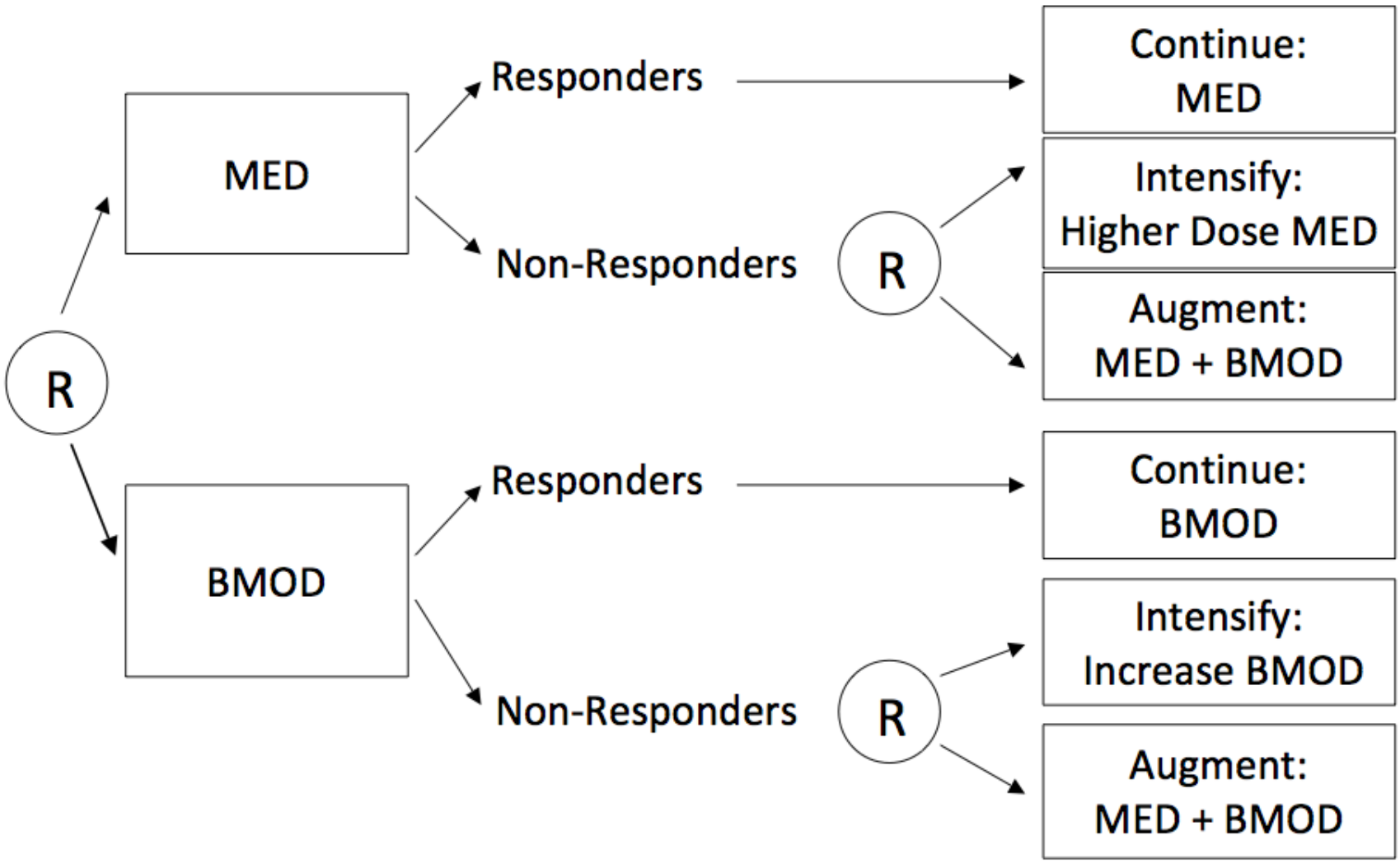
ADHD Treatment in Children Ages 6-12

- Both medication (MED) and behavioral modification (BMOD) have been shown to be efficacious
- However, there is much debate on whether first-line intervention should be pharmacological of behavioral, especially in younger children
- Further, there is a need for a ”rescue treatment” if the first treatment does not go well because 20-50% of children do not substantially improve on BMOD or MED
- So important questions for clinical practice include
  “What treatment do we begin with: BMOD or MED?”
  ”Among non-responders, what second treatment is best?”

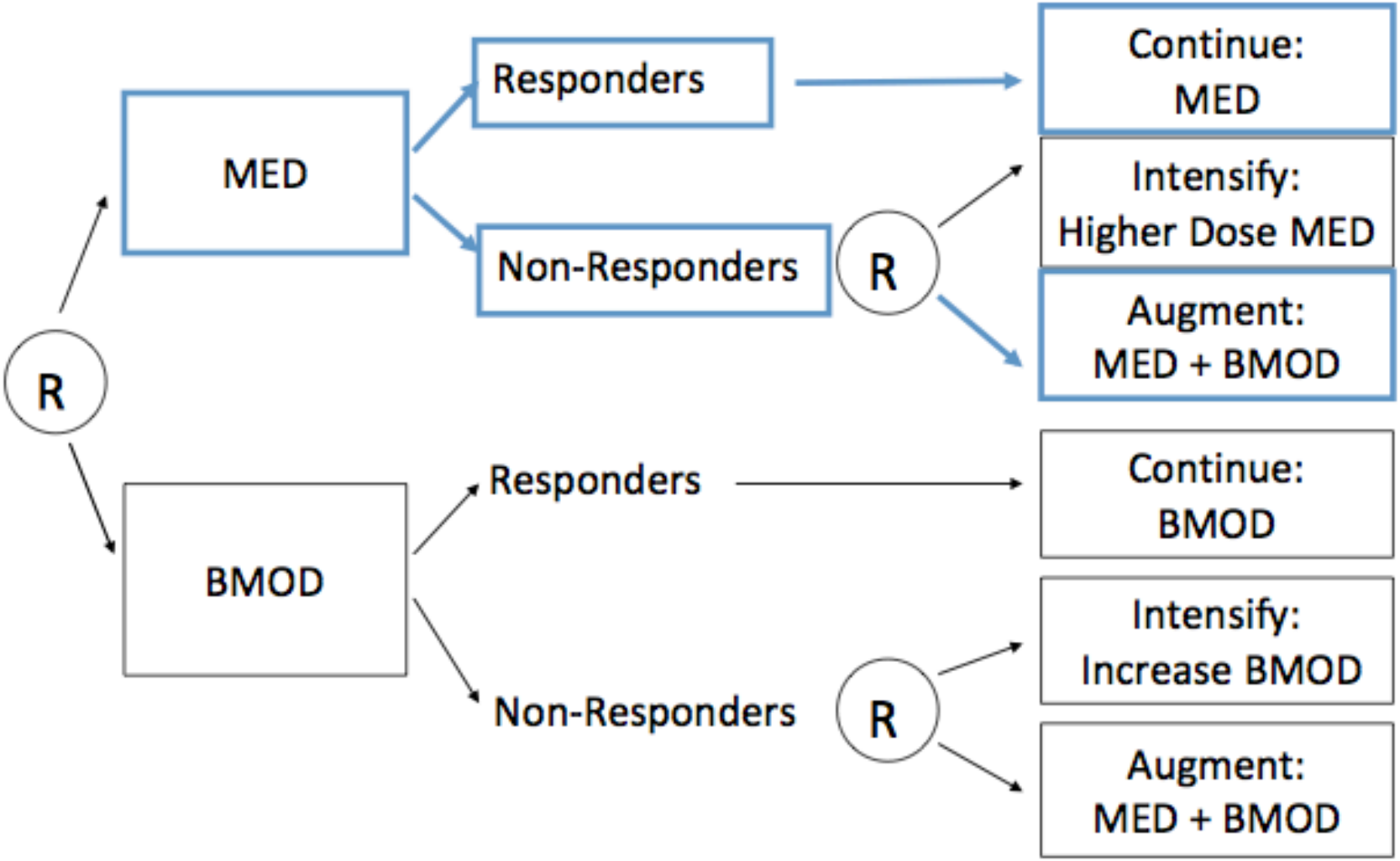
Concrete Example of a SMART: Child ADHD

PI: William Pelham, PhD, Florida International University

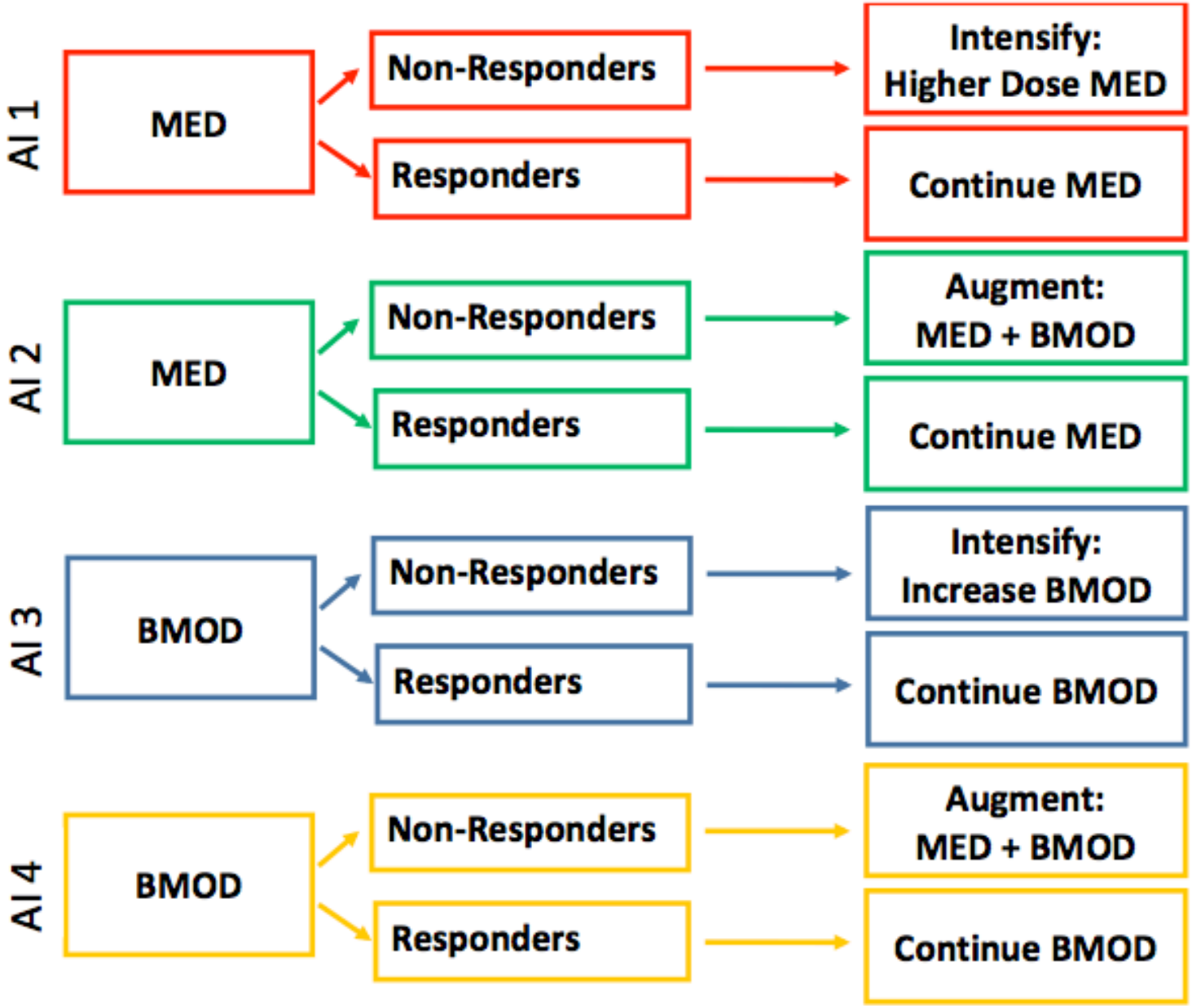
$N = 153$, 8 month study, Monthly non-response ($ITB < 0.75$ and $IRS > 1$ domain)



One of Four Adaptive Interventions Within the SMART



4 Embedded Adaptive Interventions in this SMART



SMART DESIGN PRINCIPLES

SMART Design Principles

- KISS Principle: Keep It Simple, Straightforward
- Power for simple important primary hypotheses
- Take Appropriate steps to develop a more deeply-individualized (optimized) Adaptive Intervention

Keep It Simple, Straightforward

Overarching Principle

At each stage, or critical decision point,...

- Restrict class of treatment options *only* by ethical, feasibility, or strong scientific considerations
- If you do restrict randomizations, use low dimensional summary to restrict subsequent treatments
  - Use binary responder status
  - Should be easy to use in actual clinical practice
- Collect additional, auxiliary time-varying measures
  - To develop a more deeply-tailored Adaptive Intervention
  - Think time-varying effect moderators

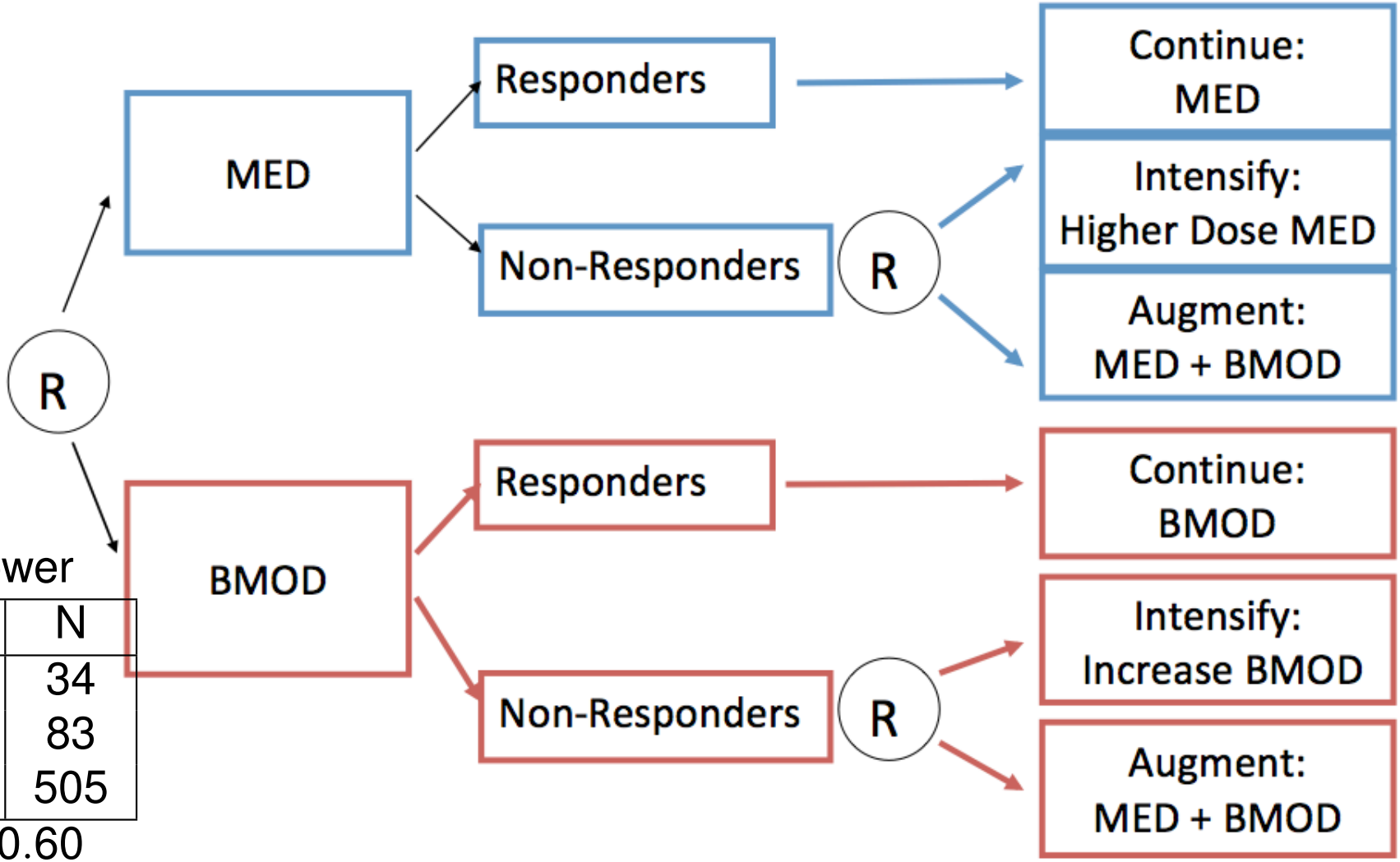
SMART Design: Primary Aims

Choose a **simple primary aim/question** that aids development of an adaptive intervention.

Sample size for the SMART chosen based on the hypothesis test associated with this aim (e.g., use standard $\alpha = 5\%$).

Primary Aim Example 1

What is the effect of starting with BMOD vs MED on longitudinal outcomes?



Power

ES	N
0.8	34
0.5	83
0.2	505

$\rho = 0.60$

$\alpha = 0.05$

$\beta = 0.20$

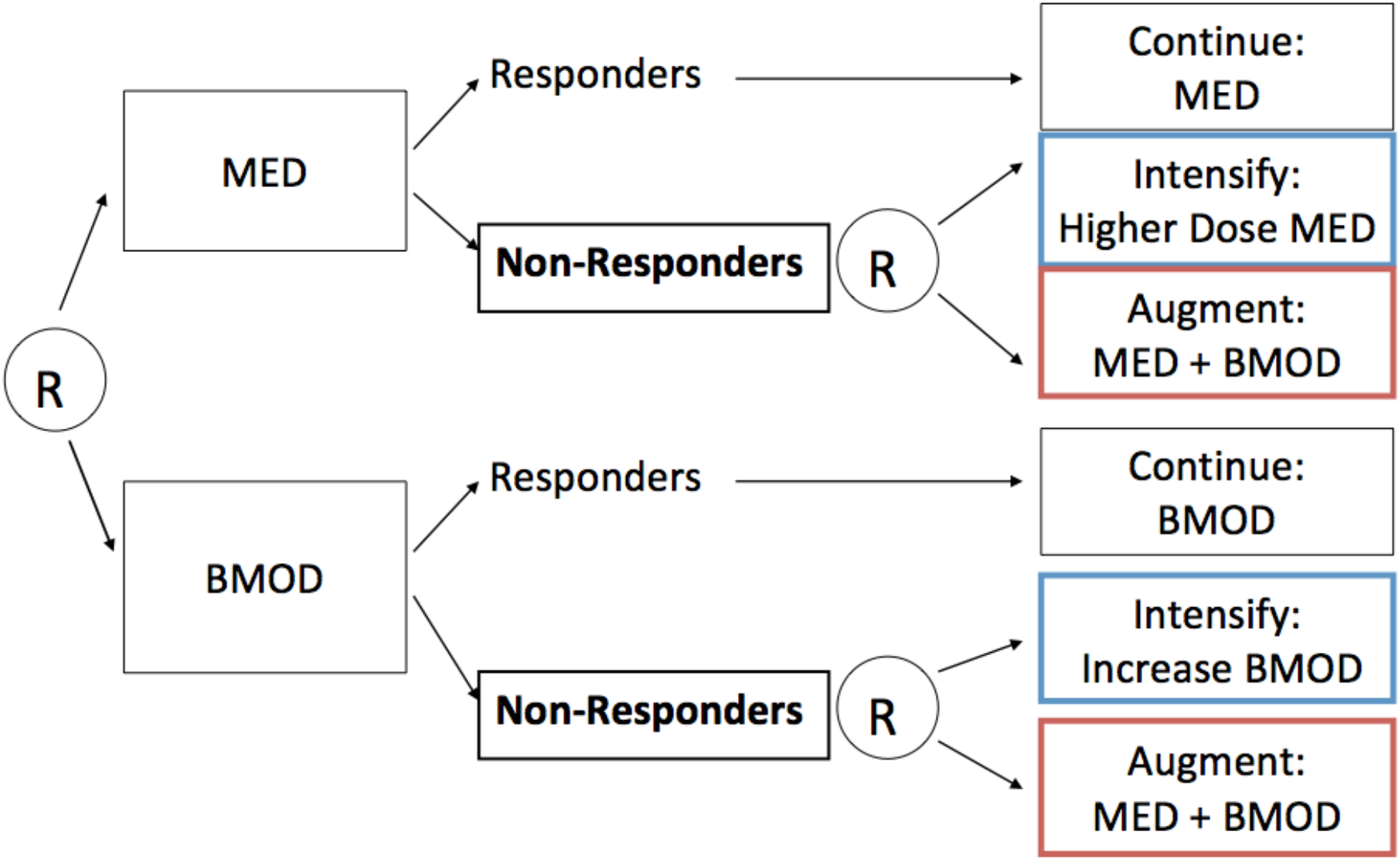
SMART Design: Secondary Aims

Choose **secondary aims/questions** that further develop the Adaptive Intervention and take advantage of sequential randomization to eliminate confounding.

You may propose to test these hypotheses at, say, $\alpha = 10\%$.

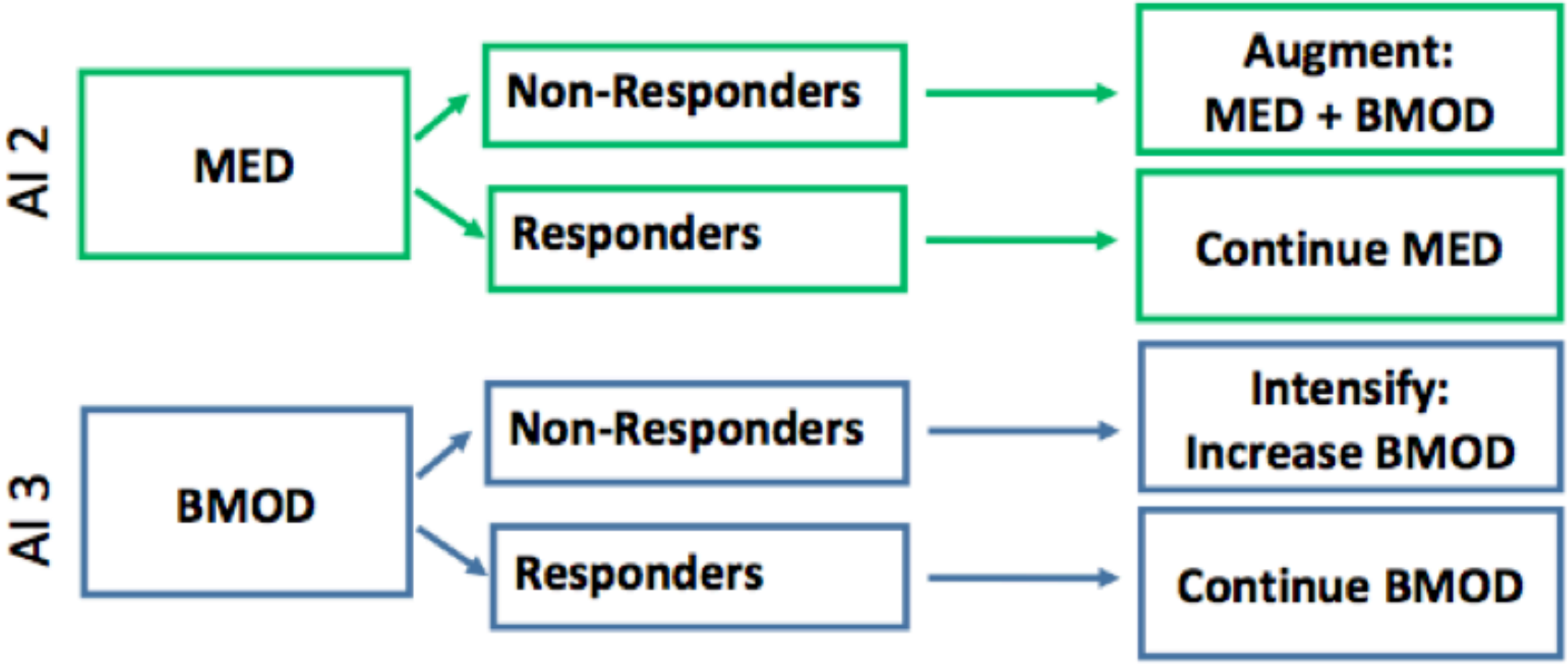
Secondary Aim Example 1

Among non-responders, is it better to INTENSIFY vs AUGMENT?



Secondary Aim Example 2

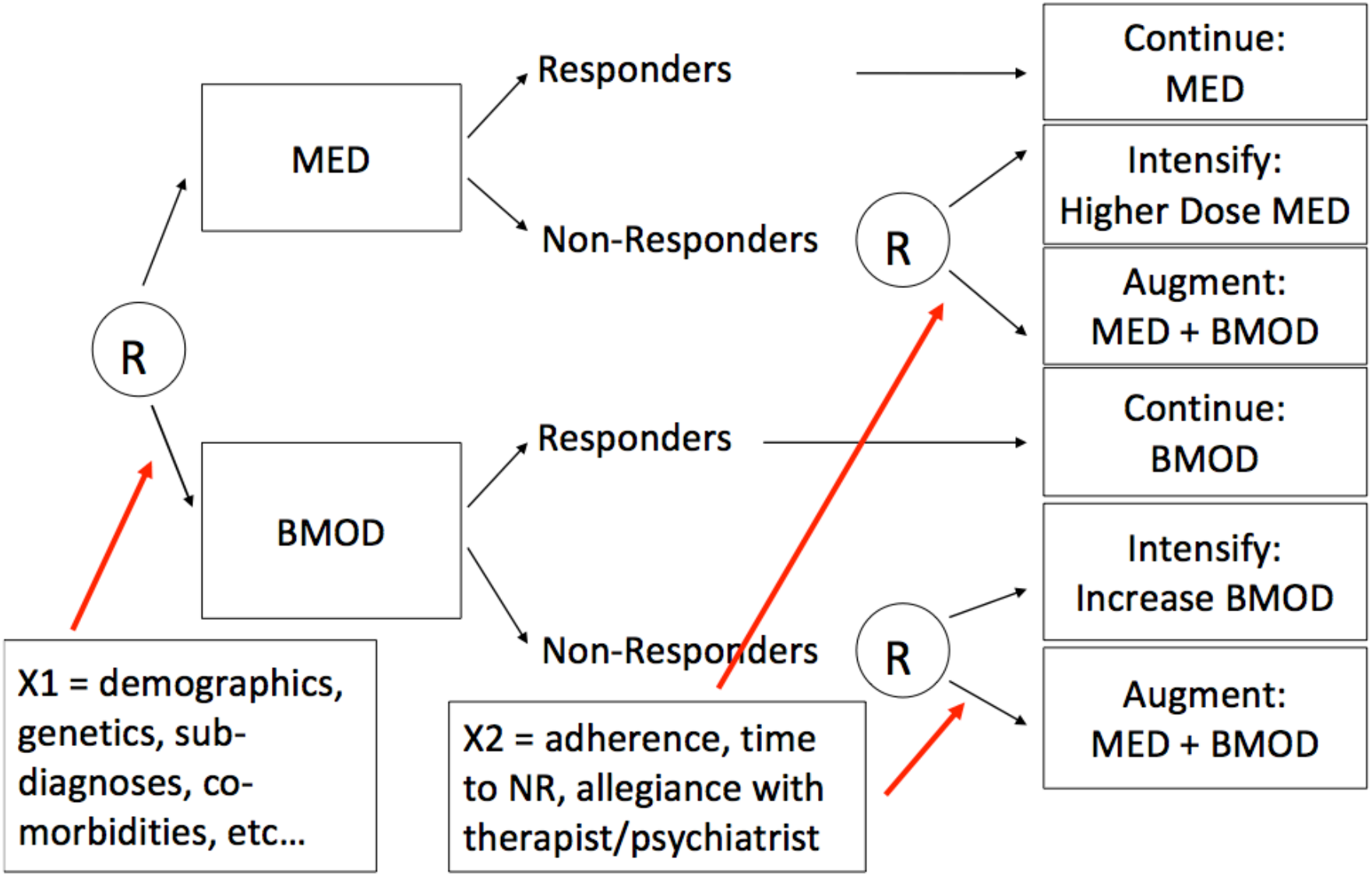
Is there a difference between two of the embedded adaptive interventions?



Sample size calculators exist for this; see Oetting, Levy, Weiss, and Murphy 2011.

Secondary Aim Example 3

Build a more deeply tailored adaptive intervention (go beyond the 4 embedded adaptive interventions).



TAKE HOME POINTS

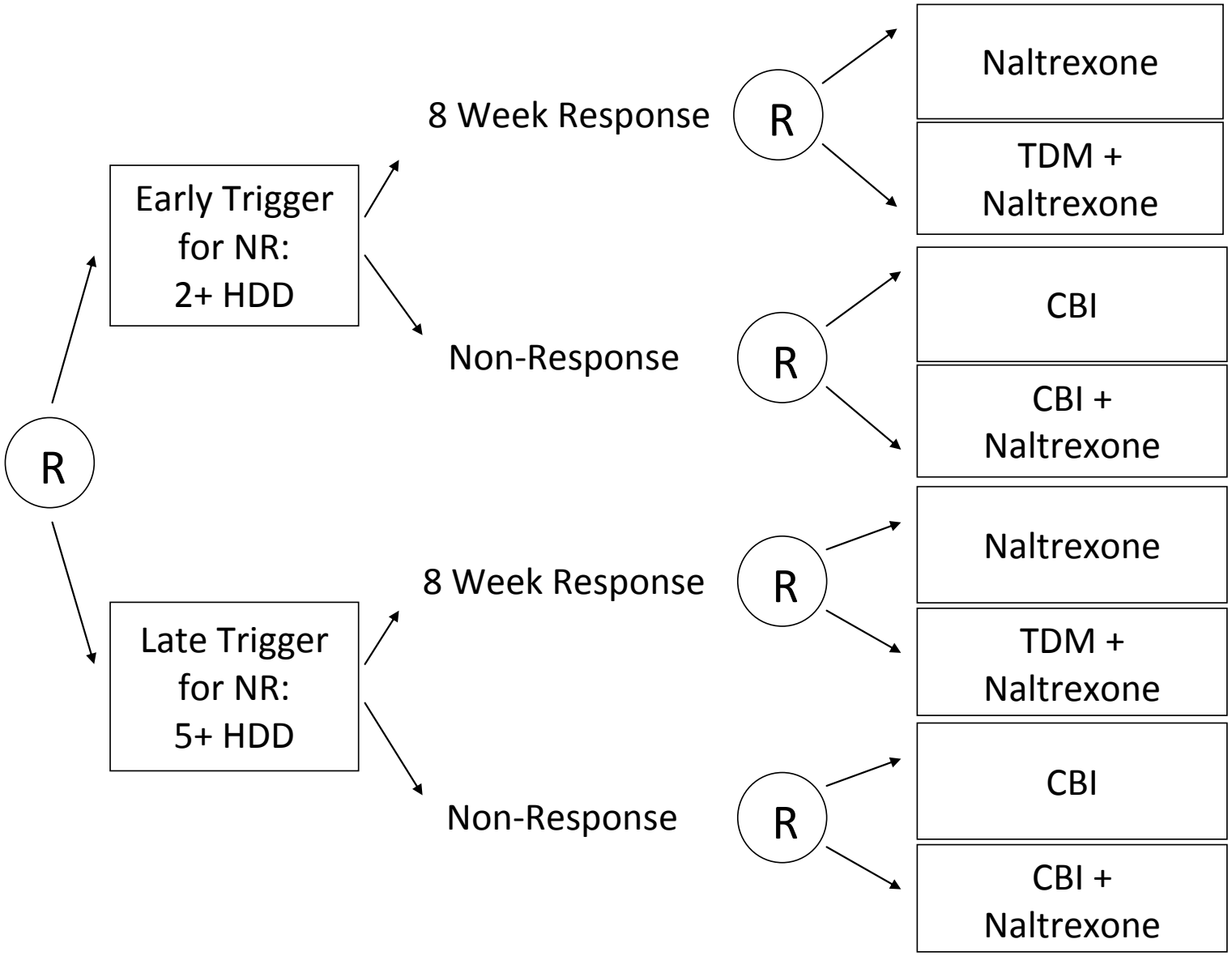
Take Home the Following

- SMARTs are not Adaptive Trial Designs (Confusing!)
- Adaptive Interventions individualize treatment up-front and throughout
- Adaptive Interventions are guides for clinical practice
- SMARTs are used to **build** better Adaptive Interventions
  - Next trial: SMART-optimized Adaptive Intervention vs. state-of-the-art treatment
- SMARTs do not necessarily require larger sample sizes

OTHER EXAMPLE SMARTS

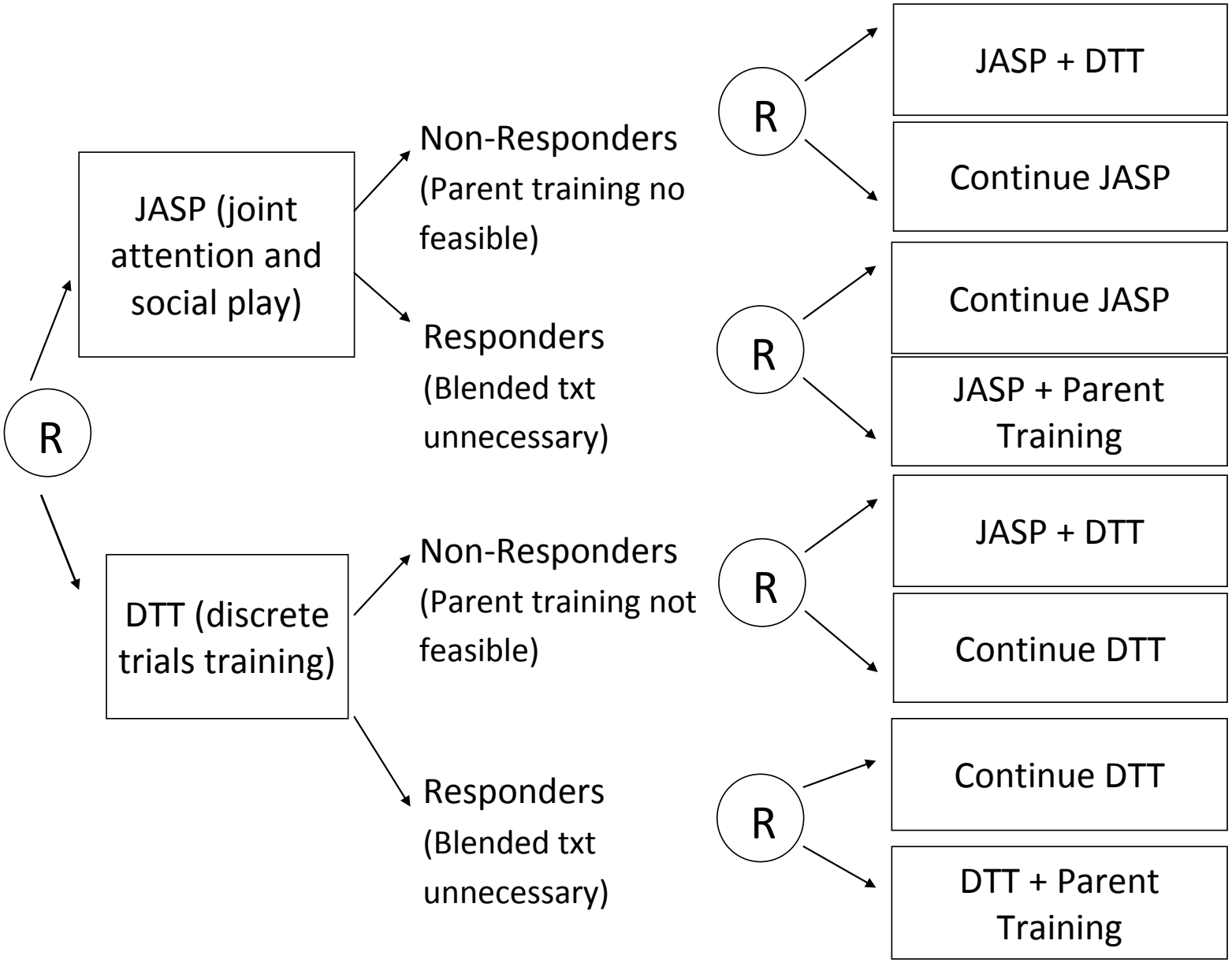
Treatment for Alcohol Dependence

PI: Oslin, University of Pennsylvania



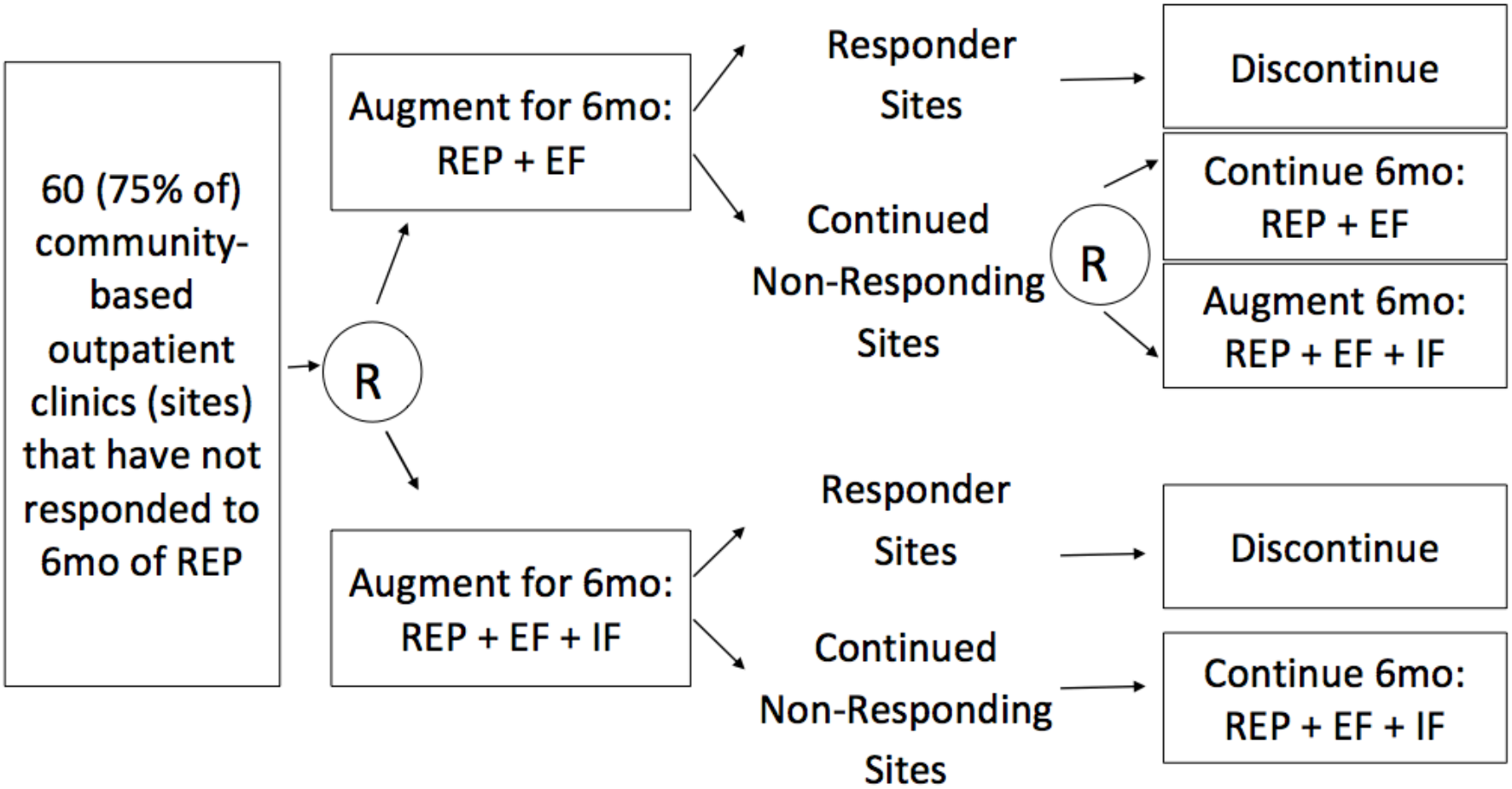
Interventions for Minimally Verbal Children with Autism

PI: Kasari(UCLA), Kaiser(Vanderbilt), Smith(Rochester), Lord(Cornell), Almirall(Mich)



Adaptive Implementation Intervention in Mental Health

PI: Kilbourne; Co-I: Almirall (Aim is to improve the uptake of a psychosocial intervention for mood disorders; REP actually used in HIV to adopt EBPs by AIDS service orgs)



Thank you! Questions?

Find papers on SMART:

- http://www.lsa.stat.umich.edu/∼samurphy/ (Susan Murphy)
- http://methcenter.psu.edu (Linda Collins)

More papers and these slides on my website (Daniel Almirall):

- http://www-personal.umich.edu/∼dalmiral/

Email me with questions about this presentation:

- Daniel Almirall: dalmiral@umich.edu

Extra Slides

Hypothesis-generating Observational Studies

Post-hoc Analyses Useful for Building Adaptive Interventions

- Give examples of different observational study questions they can examine using data from a previous 2-arm RCT
- Standard observational study caveats apply:
  - No manipulation usually means lack of heterogeneity in txt options (beyond what is controlled by experimentation in original RCT)
  - Some RCTs use samples that are too homogeneous
  - Confounding by observed baseline and time-varying factors
  - Unobserved, unknown, unmeasured confounding by baseline and time-varying factors

Hypothesis-generating Observational Studies

Post-hoc Analyses Useful for Building Adaptive Interventions

- There exists a literature for examining the impact of time-varying treatments in observational studies
  - Marginal Structural Models (Robins, 1999; Bray, Almirall, et al., 2006) to examine the marginal impact of observed time-varying sequences of treatment
  - Structural Nested Mean Models (Robins, 1994; Almirall, et al., 2010, 2011) to examine time-varying moderators of observed time-varying sequences of treatment
  - Marginal Mean Models (Murphy, et al., 2001): to examine the impact of observed adaptive interventions

Early precursors to SMART

- CATIE (2001) Treatment of Psychosis in Patients with Alzheimer's
- CATIE (2001) Treatment of Psychosis in Patients with Schizophrenia
- STAR*D (2003) Treatment of Depression

Other Alternatives

- Piecing Together Results from Multiple Trials
  - Choose best first-line treatment on the basis of a two-arm RCT; then choose best second-line treatment on the basis of another separate, two-arm RCT
  - Concerns: delayed therapeutic effects, and cohort effects
- Observational (Non-experimental) Comparisons of AIs
  - Using data from longitudinal randomized trials
  - May yield results that inform a SMART proposal
  - Understand current treatment sequencing practices
  - Typical problems associated with observational studies
- Expert Opinion

Why Not Use Multiple Trials to Construct an AI

Three Concerns about Using Multiple Trials as an Alternative to a SMART

1. Concern 1: Delayed Therapeutic Effect
2. Concern 2: Diagnostic Effects
3. Concern 3: Cohort Effects

All three concerns emanate from the basic idea that constructing an adaptive intervention based on a myopic, local, study-to-study point of view may not be optimal.

Why Not Use Multiple Trials to Construct an AI

Concern 1: Delayed Therapeutic Effects, or Sequential Treatment Interactions

Positive Synergy Btwn First- and Second-line Treatments

Tapering off medication after 12 weeks of use may not appear best initially, but may have enhanced long term effectiveness when followed by a particular augmentation, switch, or maintenance strategy.

Tapering off medication after 12 weeks may set the child up for better success with any one of the second-line treatments.

Why Not Use Multiple Trials to Construct an AI

Concern 1: Delayed Therapeutic Effects, or Sequential Treatment Interactions

Negative Synergy Btwn First- and Second-line Treatments

Keeping the child on medication an additional 12 weeks may produce a higher proportion of responders at first, but may also result in side effects that reduce the variety of subsequent treatments available if s/he relapses.

The burden associated with continuing medication an additional 12 weeks may be so high that non-responders will not adhere to second-line treatments.

Why Not Use Multiple Trials to Construct an AI

Concern 2: Diagnostic Effects

Tapering off medication after 12 weeks initial use may not produce a higher proportion of responders at first, but may elicit symptoms that allow you to better match subsequent treatment to the child.

The improved matching (personalizing) on subsequent treatments may result in a better response overall as compared to any sequence of treatments that offered an additional 12 weeks of medication after the initial 12 weeks.

Why Not Use Multiple Trials to Construct an AI

Concern 3: Cohort Effects

- Children enrolled in the initial and secondary trials may be different.
- Children who remain in the trial(s) may be different.
- Characteristics of adherent children may differ from study to study.
- Children that know they are undergoing adaptive interventions may have different adherence patterns.

Bottom line: The population of children we are making inferences about may simply be different from study-to-study.