

# Developing Adaptive Health Interventions

## Getting SMART

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# Outline

## Adaptive Interventions

What? Why?

## Sequential Multiple Assignment Randomized Trial (SMART)

What are SMARTs?

## SMART Design Principles

Keep it Simple

Choosing Primary and Secondary Hypotheses

## Discussion

# ADAPTIVE INTERVENTIONS

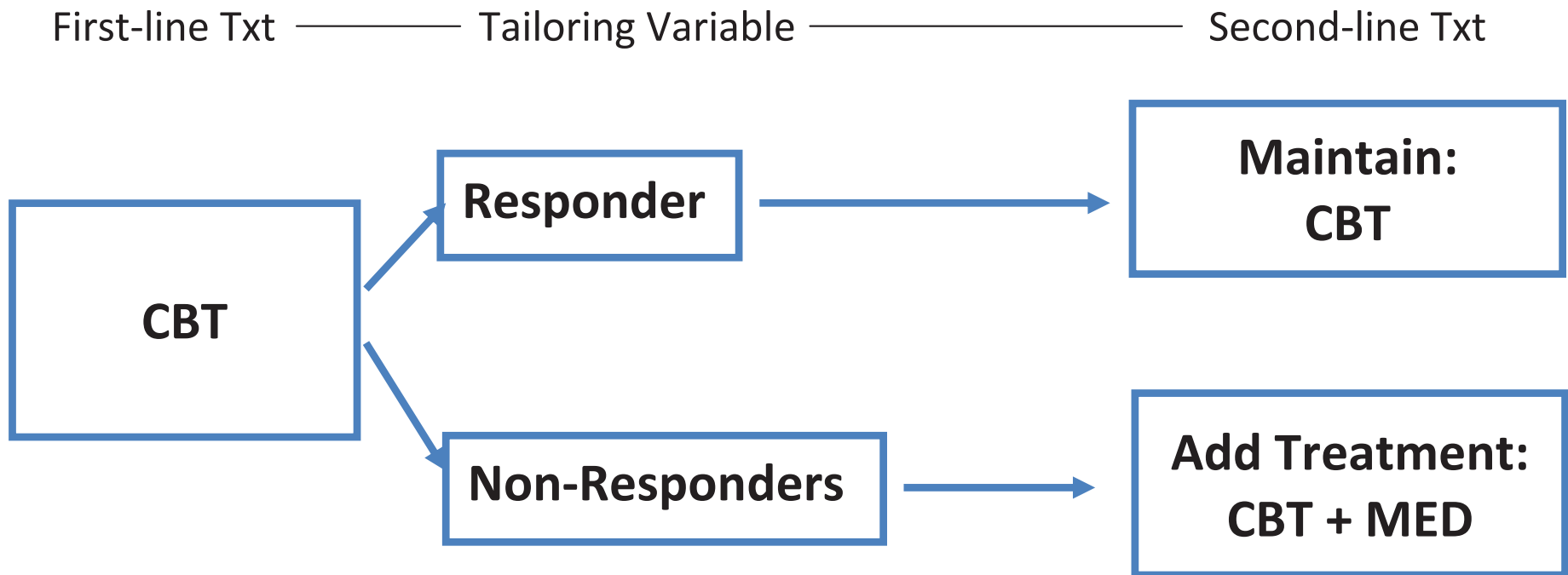
## Definition: An Adaptive Intervention is

- ▶ 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

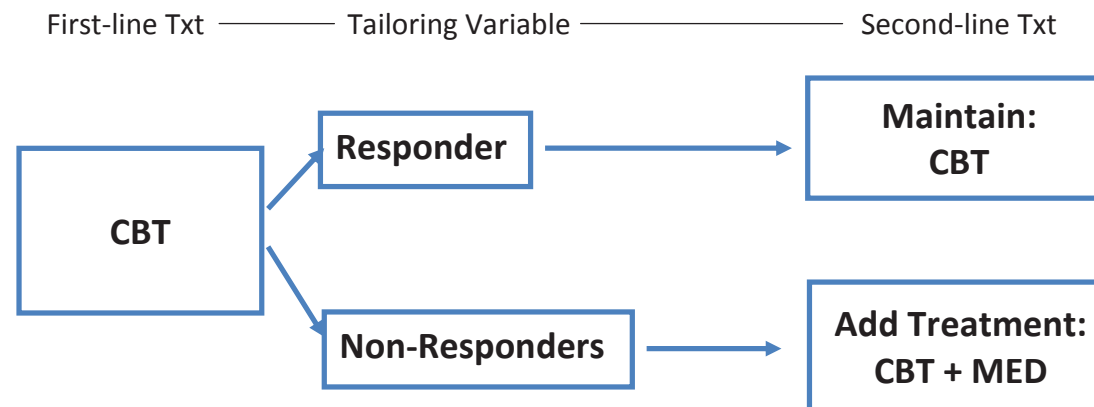
Pediatric Anxiety Example (SAD, GAD, SoP)



- ▶ 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



Also known as: dynamic treatment regimes, adaptive treatment strategies, treatment algorithms, structured treatment interruptions (HIV/AIDS), practice parameters (child psych.), ASAM PPC, stepped care intervention models...

# Why Adaptive Interventions?

Necessary because...

- ▶ Chronic nature of substance use/mental health disorders
  - ▶ Waxing and waning course (multiple relapse, recurrence)
- ▶ High patient heterogeneity in response to treatment
  - ▶ Within person (over time) differential response to treatment
  - ▶ Between person differential response to treatment
  - ▶ Ex: Not all kids need CBT+MED up front

All require sequences of treatment decisions.

# 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...

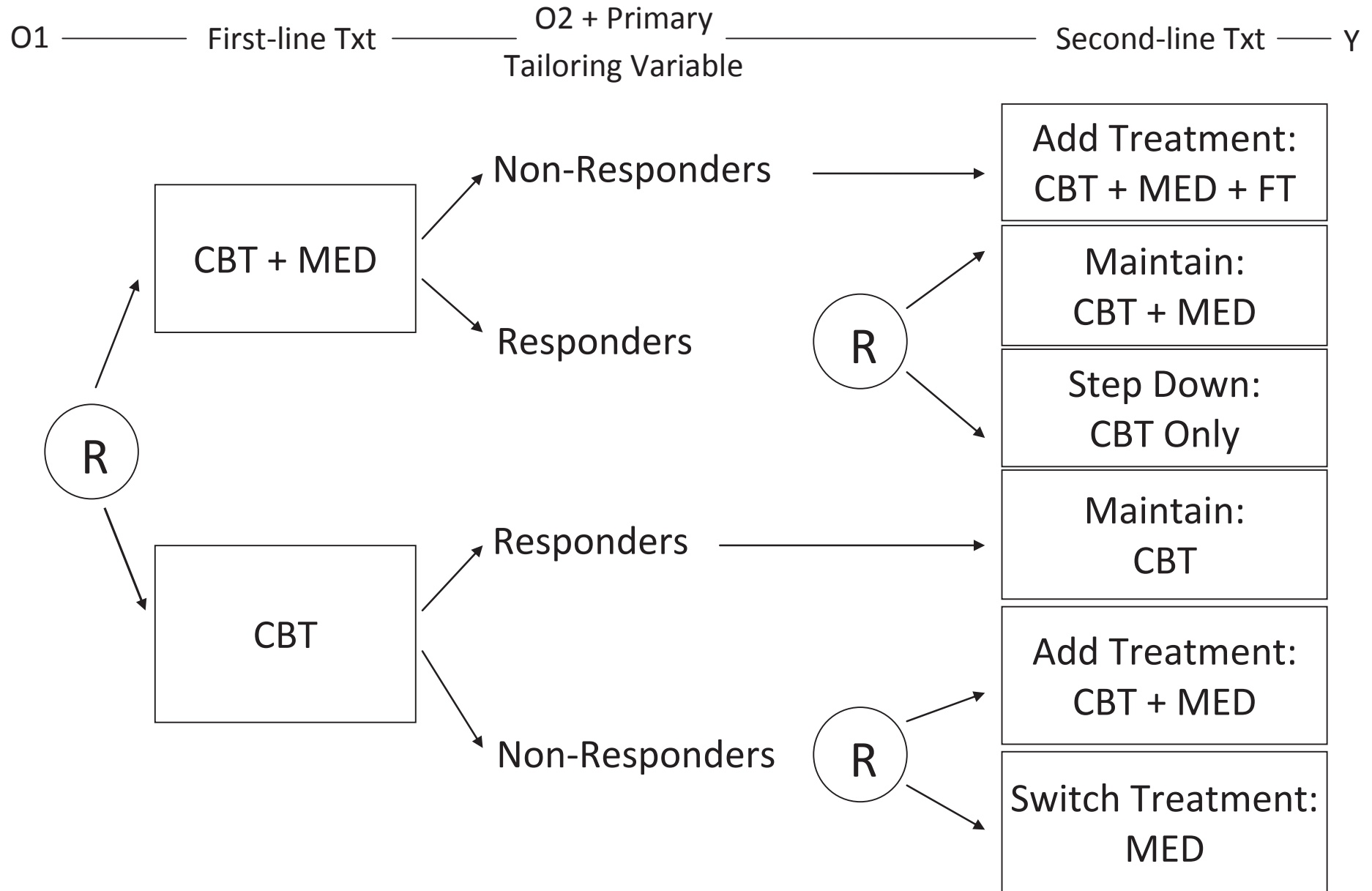
# Motivation for an Example SMART

## Child-Adolescent Anxiety Multi-modal Study (CAMS)

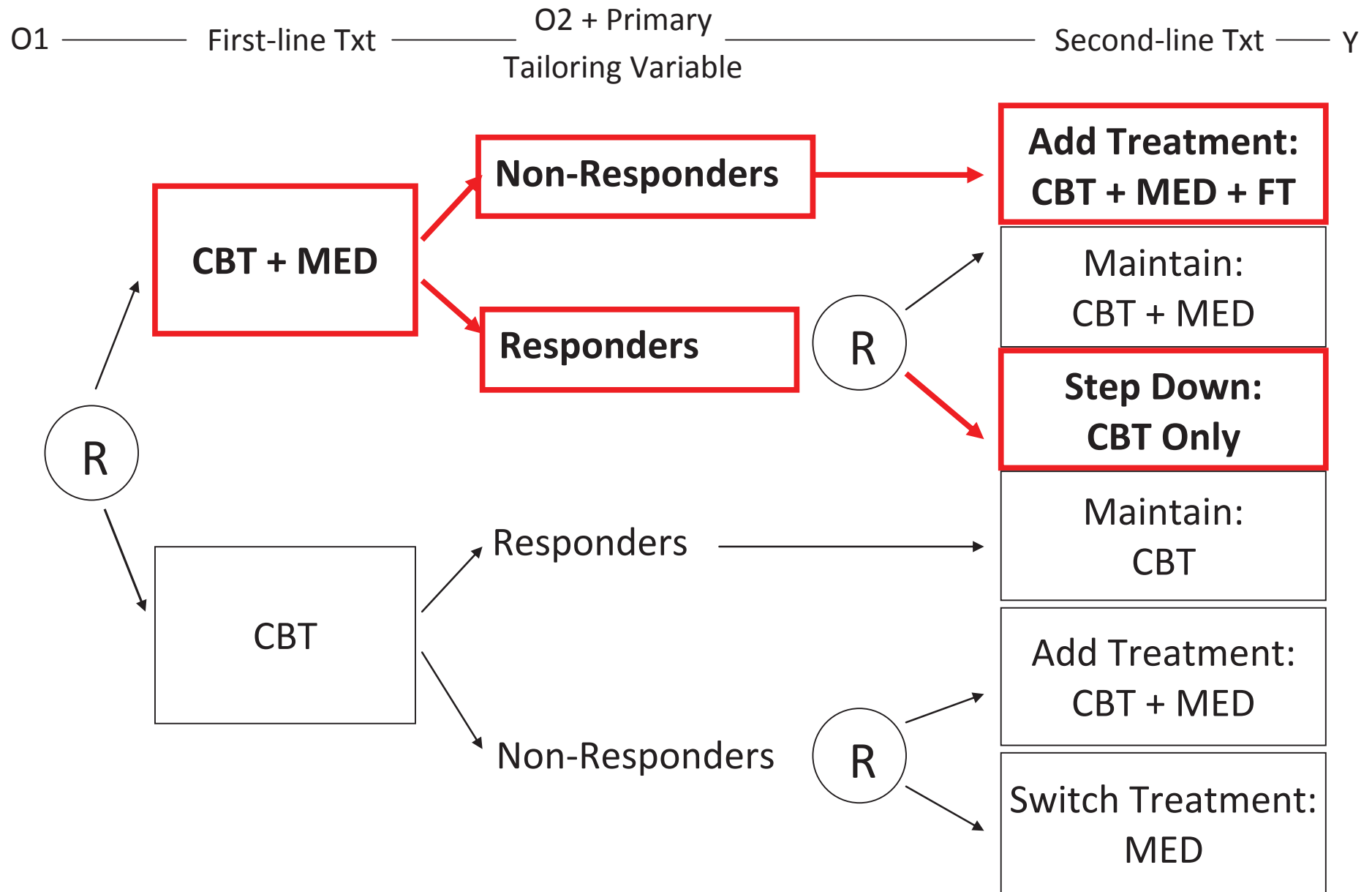
- ▶ CAMS: acute-phase, efficacy, RCT for child anxiety
- ▶ CBT+MED > MED  $\approx$  CBT > Placebo
- ▶ However, some families and clinicians remain concerned about the use of MED in this population
- ▶ So an important next question for clinical practice is  
“Can we delay the use of MED?”  
“If so, for whom?”
- ▶ Some children may do fine w/ CBT only and not need MED.

# Concrete Example of a SMART: Pediatric Anxiety

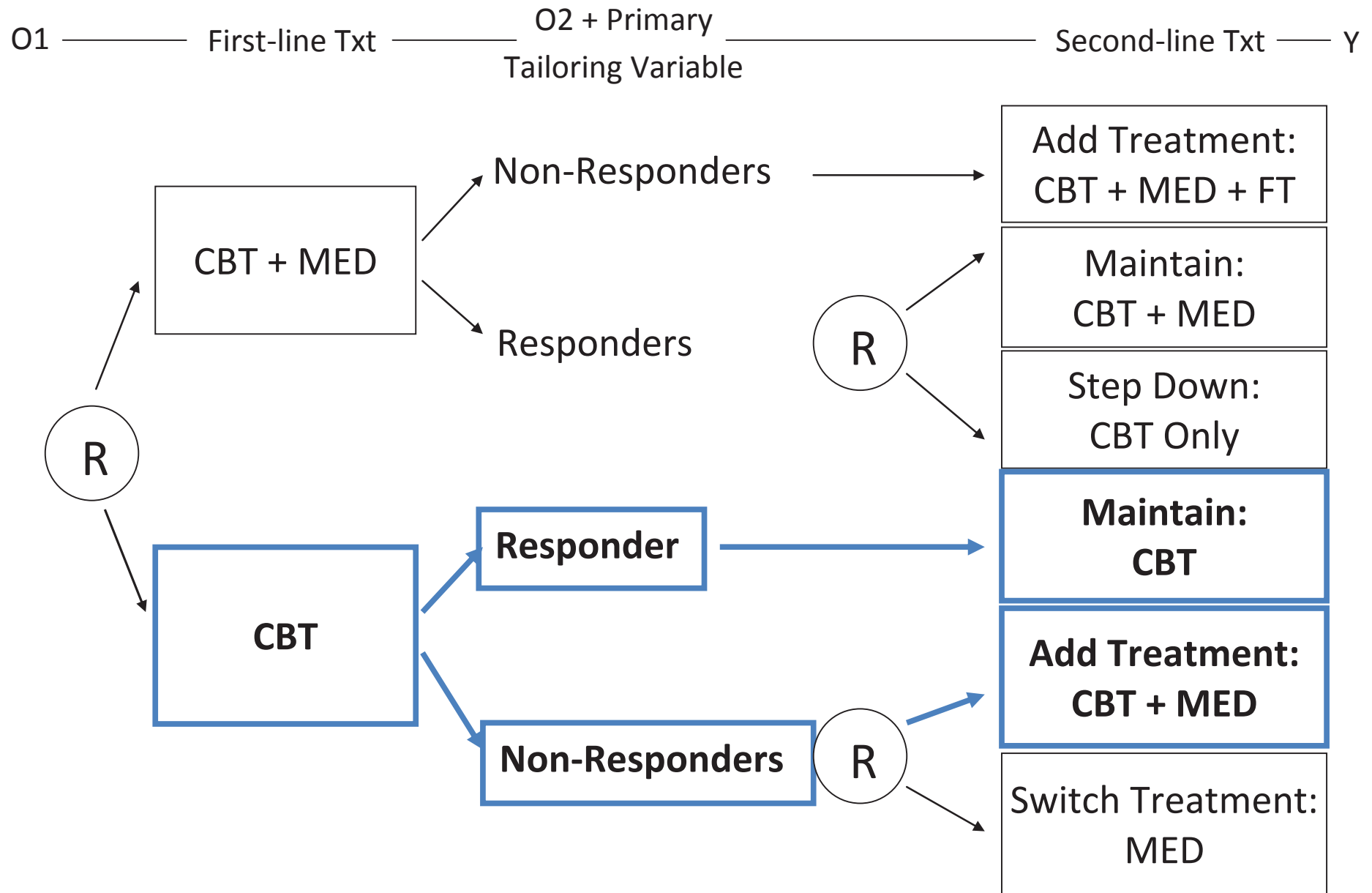
Courtesy of Scott N Compton, Duke University Medical Center



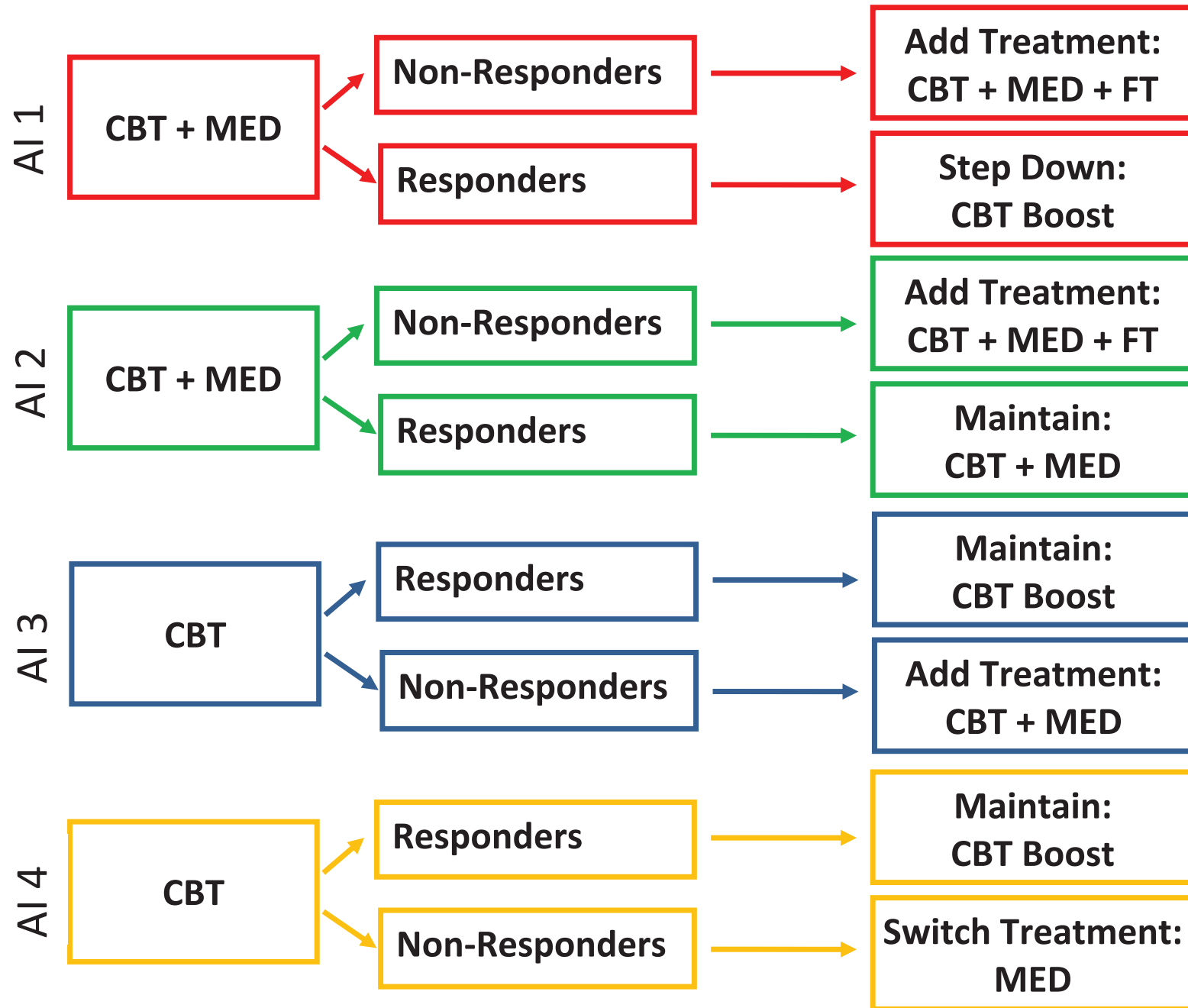
# One Adaptive Intervention Within the SMART



# Another Adaptive Intervention Within the SMART



## 4 Embedded Adaptive Interventions in this SMART



# SMART DESIGN PRINCIPLES

# SMART Design Principles

- ▶ KISS Principle: Keep It Simple, Straightforward
- ▶ Power for a simple Primary Aim
- ▶ Take Appropriate steps to develop a more richly-individualized Adaptive Intervention in Secondary Aims



# Keep It Simple, Straightforward

## Overarching Principle

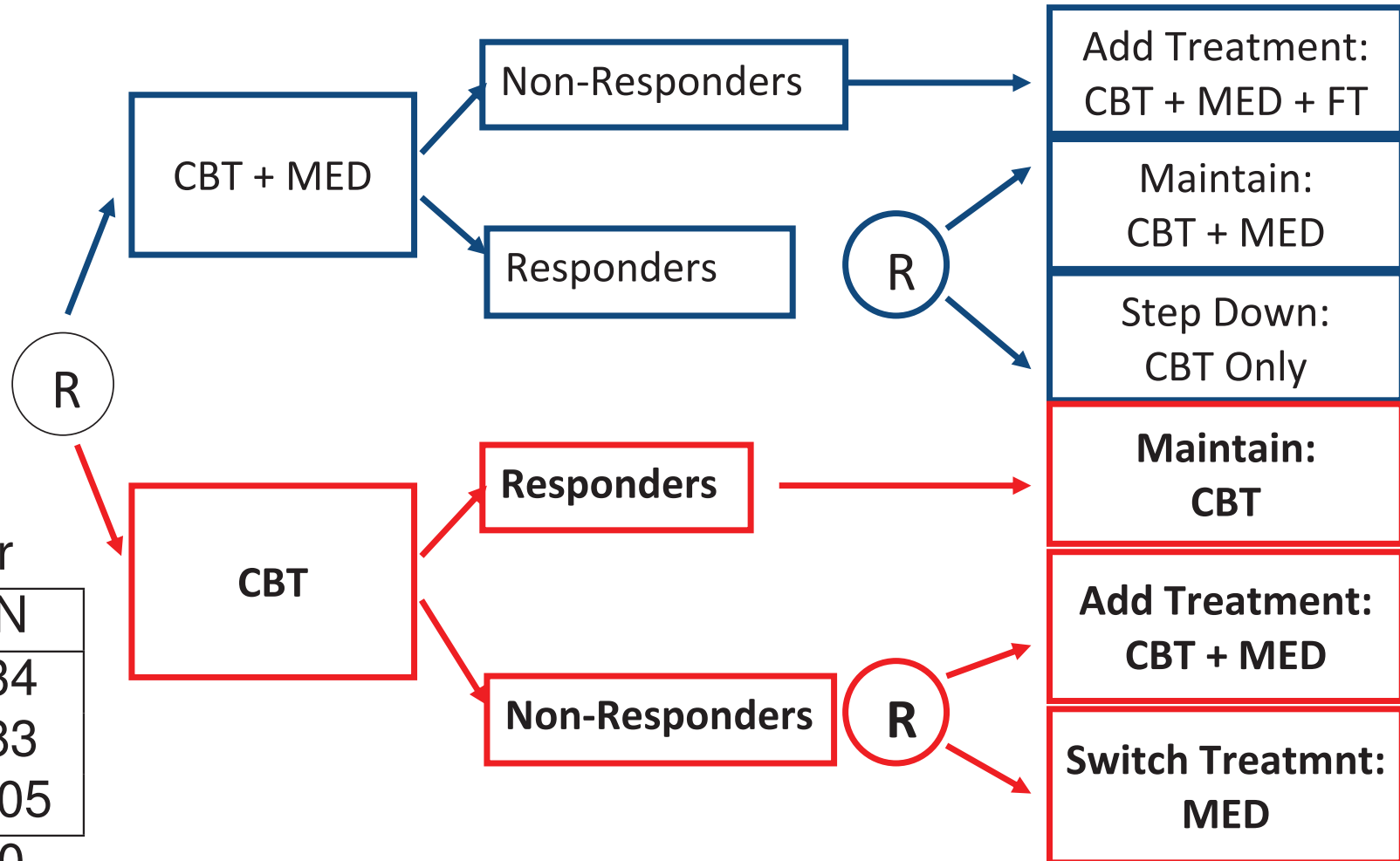
At each stage, or critical decision point,...

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

# Primary Aim Example

What is the main effect of first-line treatment? Longitudinal outcome (e.g., LMM).

O1 ——— First-line Txt ——— O2 + Primary ——— Second-line Txt ——— Y  
Tailoring Variable



Power

ES	N
0.8	34
0.5	83
0.2	505

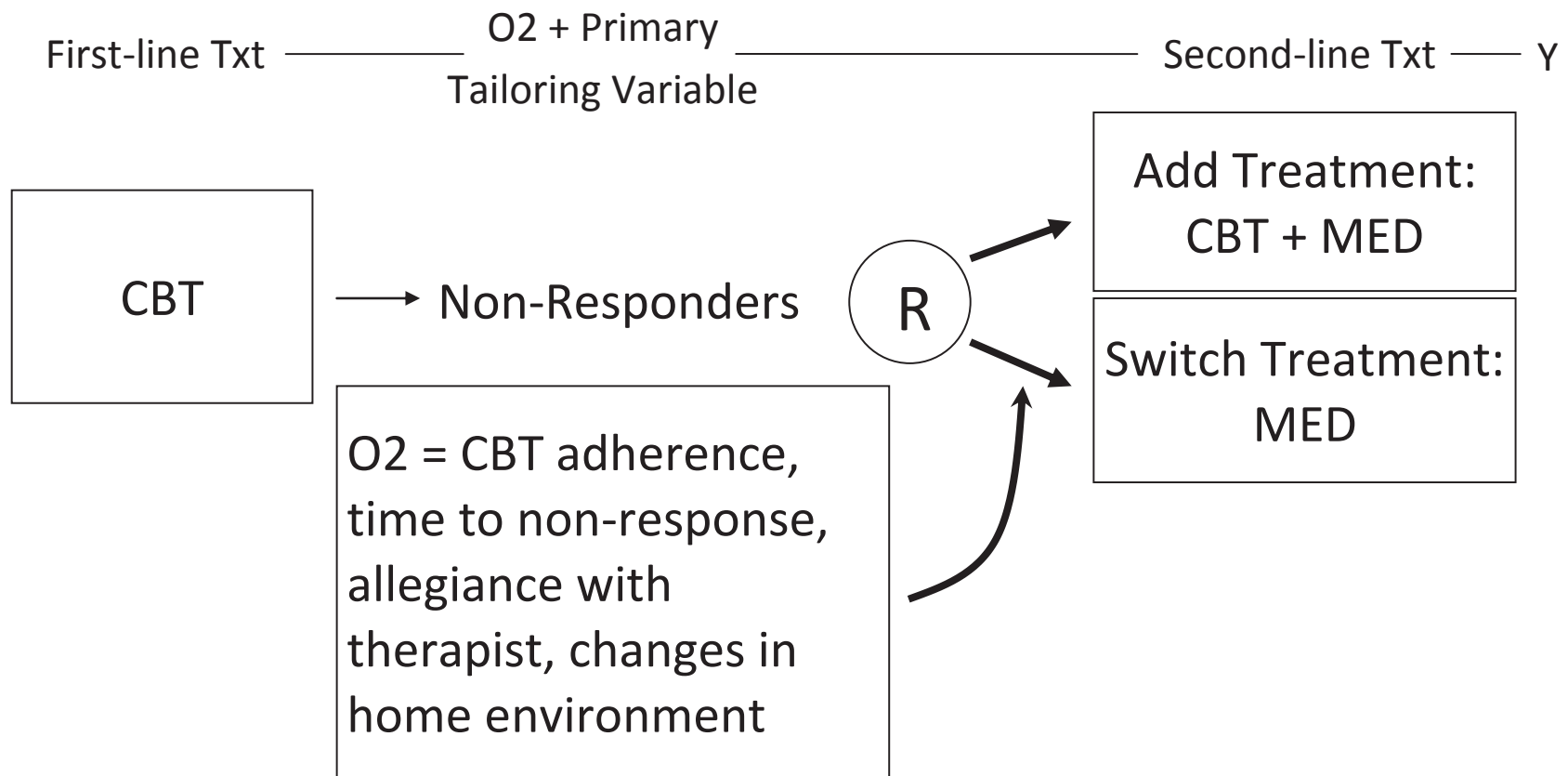
$$\rho = 0.60$$

$$\alpha = 0.05$$

$$\beta = 0.20$$

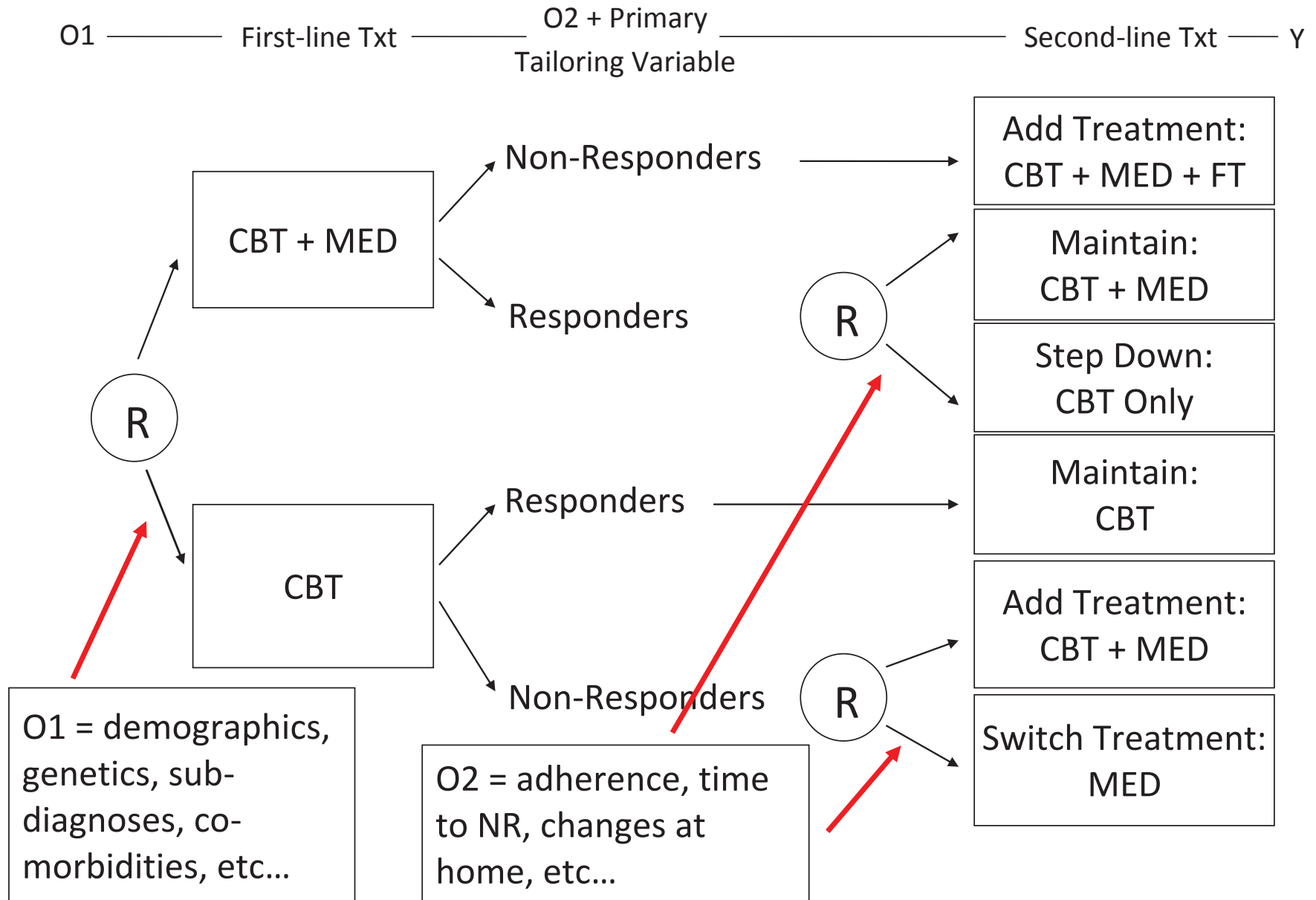
## Secondary Aim Examples 1 and 2

Best second-line treatment and second-line treatment tailoring aim.

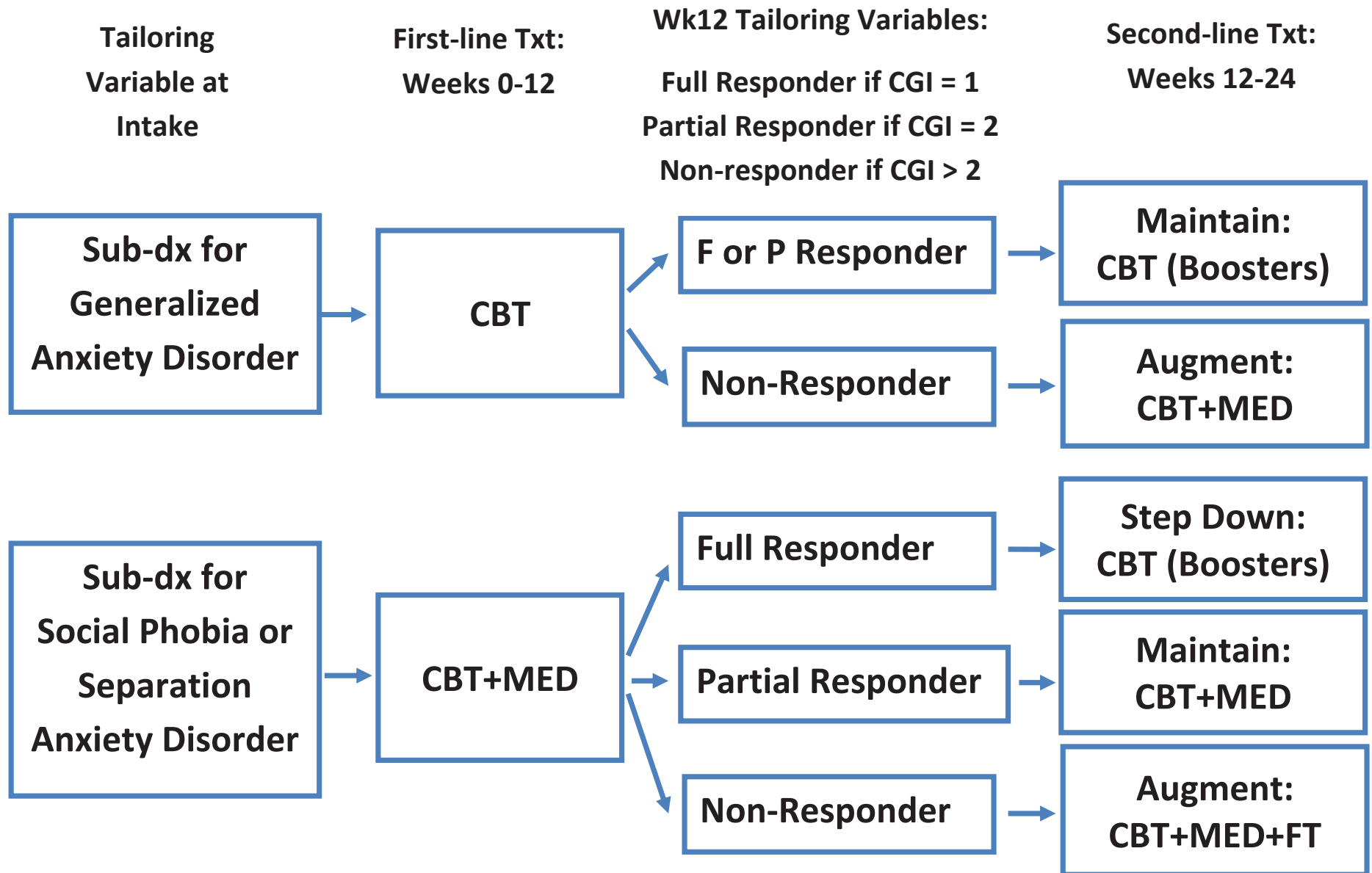


# Secondary Aim Example 3

Build a more richly-tailored adaptive intervention.



# Example: A More Richly-tailored Adaptive Intervention



# DISCUSSION

## Take Home the Following

- ▶ Adaptive Interventions are guides for clinical practice that can individualize treatment up-front and throughout
- ▶ SMARTs are used to **build** better Adaptive Interventions
- ▶ SMARTs do not necessarily require larger sample sizes

# Thank you! Questions?



Email me with questions about this presentation:

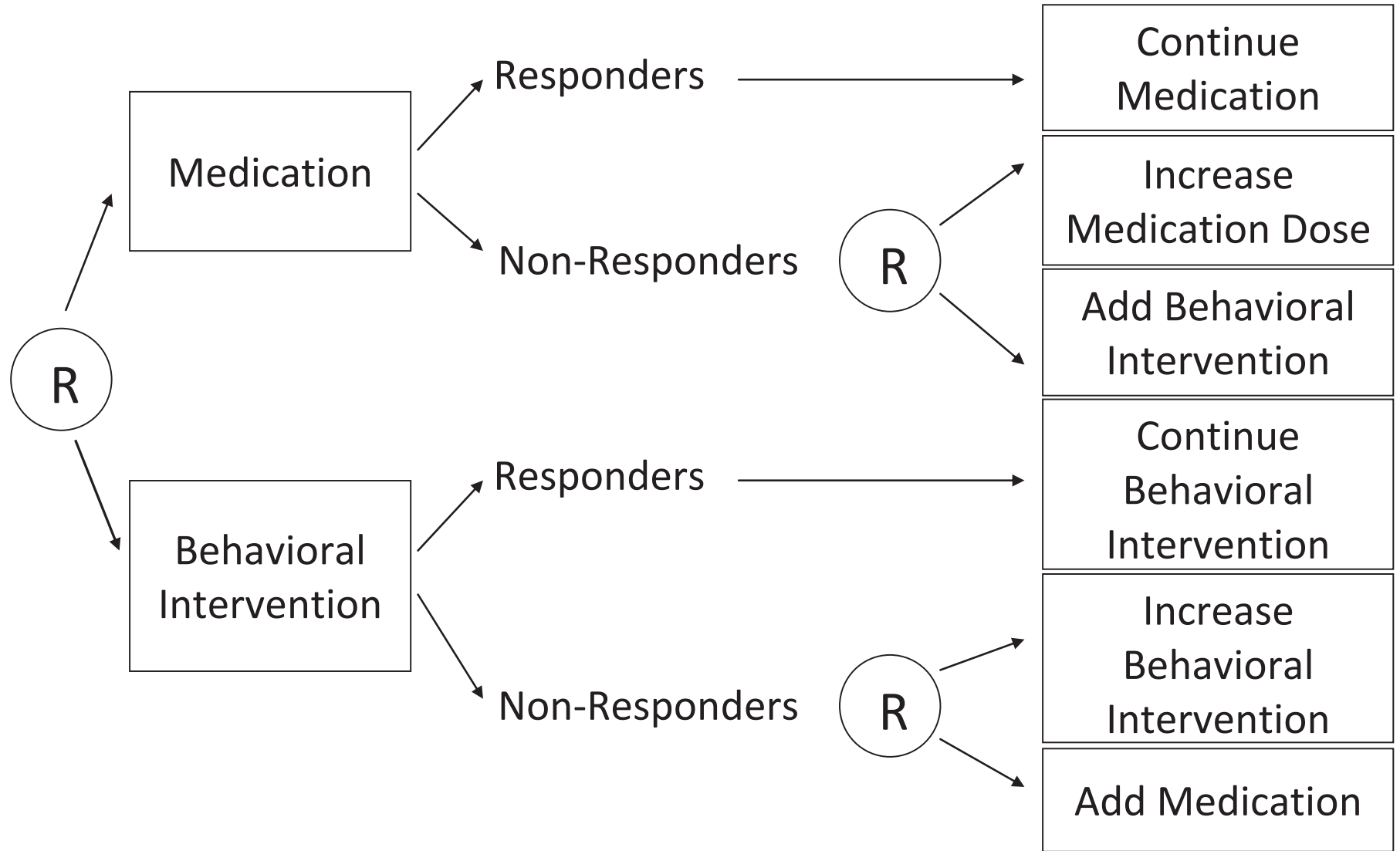
- ▶ Daniel Almirall: [dalmiral@umich.edu](mailto:dalmiral@umich.edu)



# Back Pocket Slides

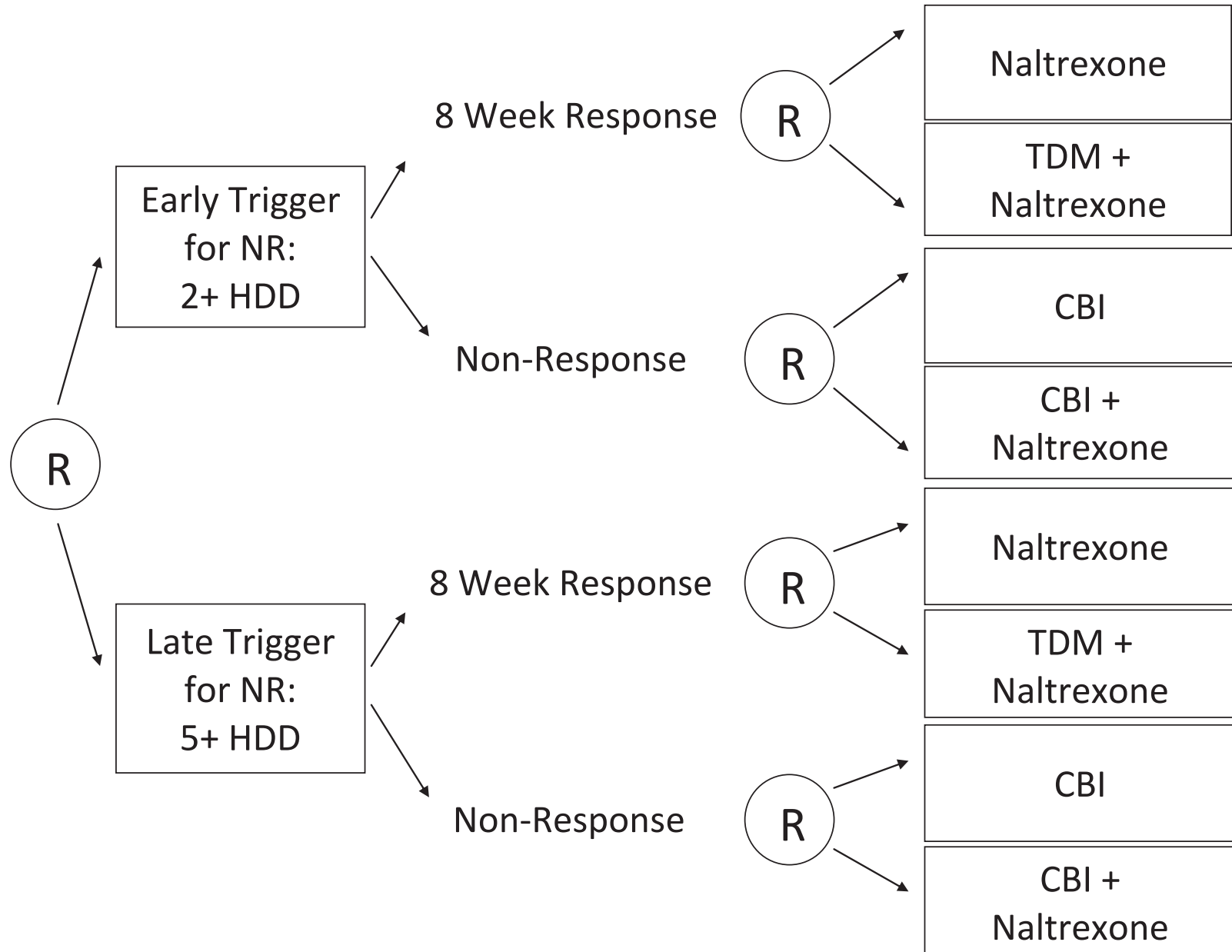
# Adaptive Treatment for Children with ADHD

PI: Pelham, Florida International University



# Treatment for Alcohol Dependence

PI: Oslin, University of Pennsylvania



# Hypothesis-generating Observational Studies

## Post-hoc Analyses Useful for Building Adaptive Interventions

- ▶ Variety of study questions can be examined 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 Als
  - ▶ 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.