Getting SMART about Developing Individualized Sequences of Health Interventions

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IMPACT Meeting - North Carolina - November 2, 2012

Outline

Adaptive Interventions
- What? Why?

Evaluating versus Building an Adaptive Intervention?

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

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

Discussion

ADAPTIVE INTERVENTIONS

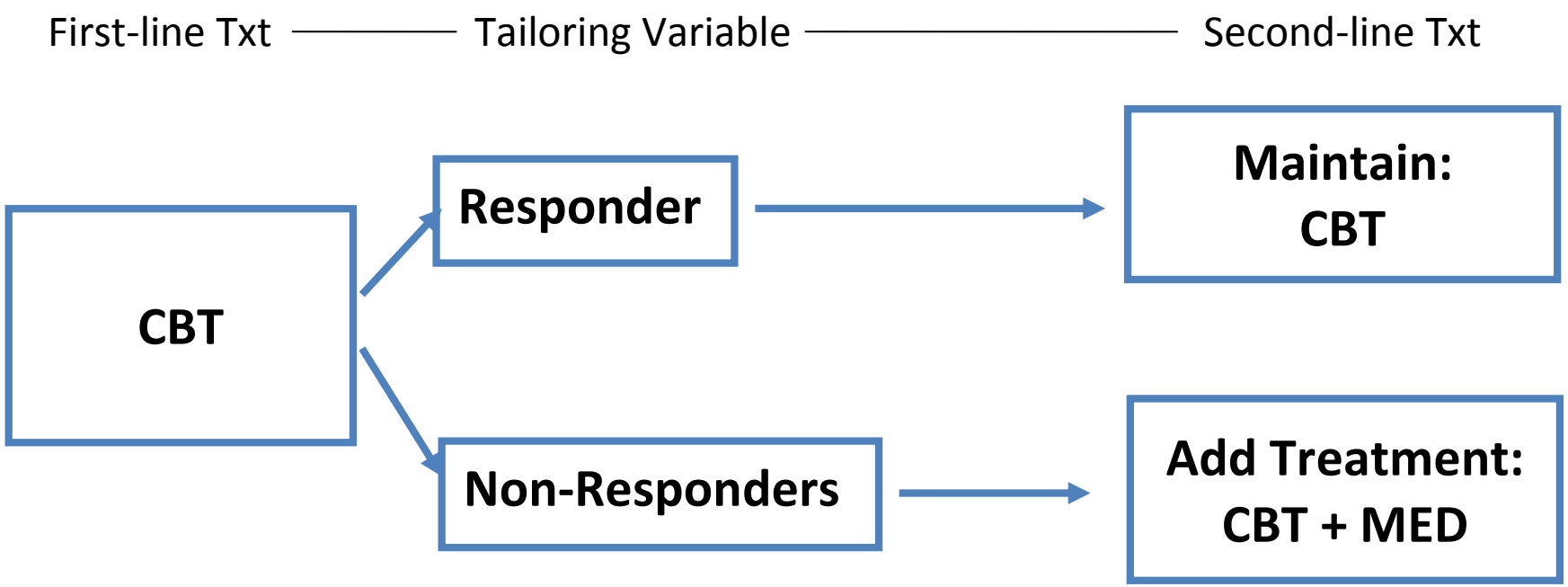
Definition: An Adaptive Intervention is

- 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

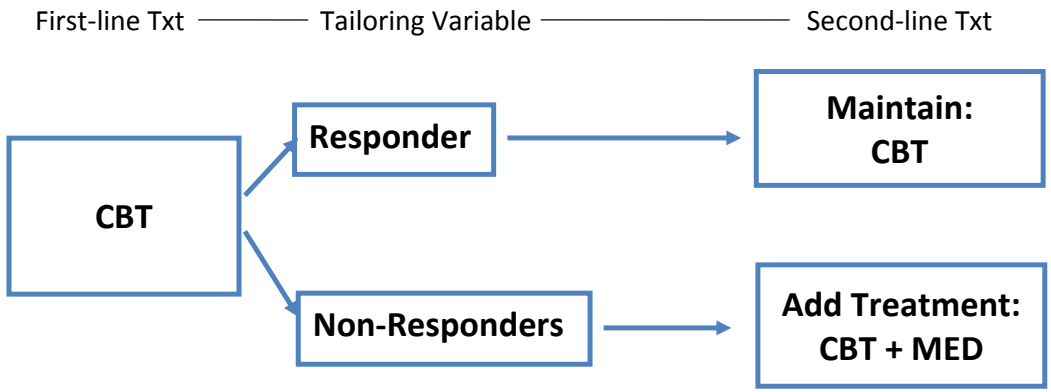
Pediatric Anxiety Example (SAD, GAD, SoP)



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

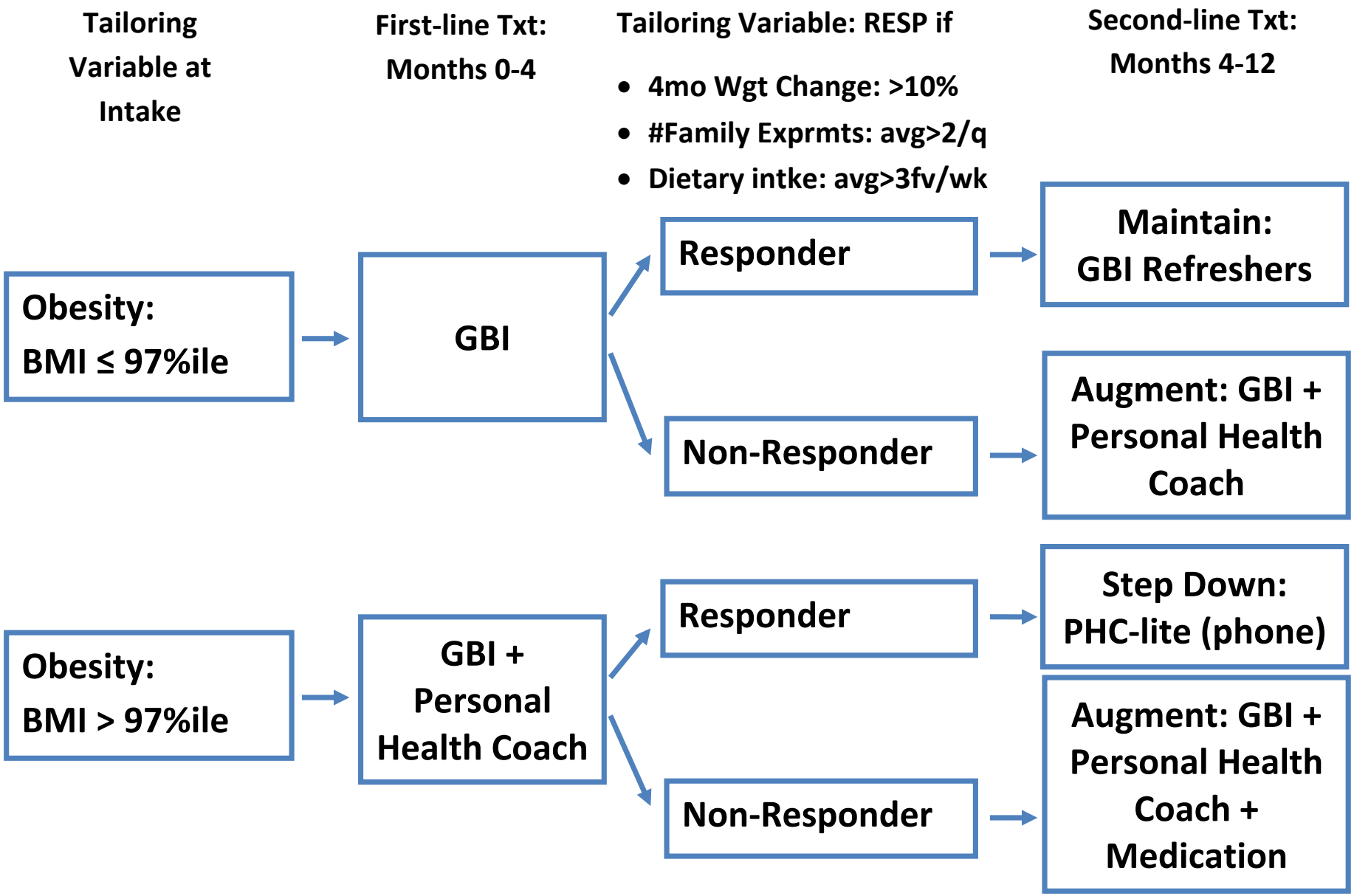
What makes up an Adaptive Intervention?

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



Adaptive interventions AKA: dynamic treatment regimes, adaptive treatment strategies, treatment algorithms, structured treatment interruptions, practice parameters, ASAM criteria...

An Adaptive Intervention in Obesity



Why Adaptive Interventions?

Necessary because...

- Nature of chronic disorders (substance use, mental health, diabetes, cancer)
  - Waxing and waning course (multiple relapse, recurrence)
  - Genetic and non-genetic factors influence course
  - Co-occuring disorders may arise
- High patient heterogeneity in response to treatment
  - Within person (over time) differential response to treatment
  - Between person differential response to treatment

All require sequences of treatment decisions.

GENERATING HYPOTHESES vs BUILDING vs EVALUATING ADAPTIVE INTERVENTIONS?

3 Different Research Questions/Aims = 3 Different Research Designs

- **Aim 1**: When **generating hypotheses** to build 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 significant effect as compared to control intervention?

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 significant effect as compared to control intervention?

		Observational Studies	Experimental Studies	
Question	Aim	e.g., 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...

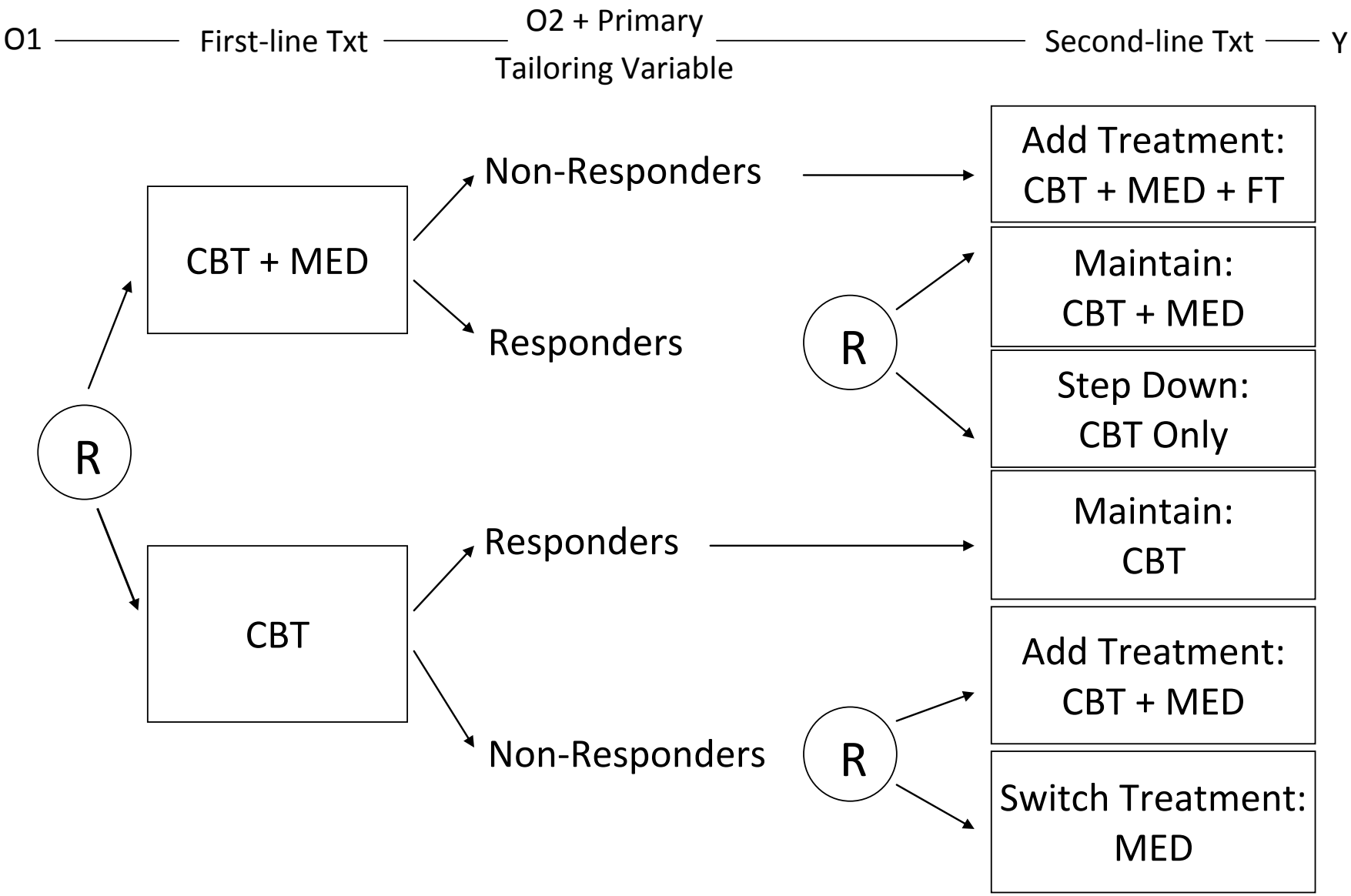
Motivation for an Example SMART

Child-Adolescent Anxiety Multi-modal Study (CAMS)

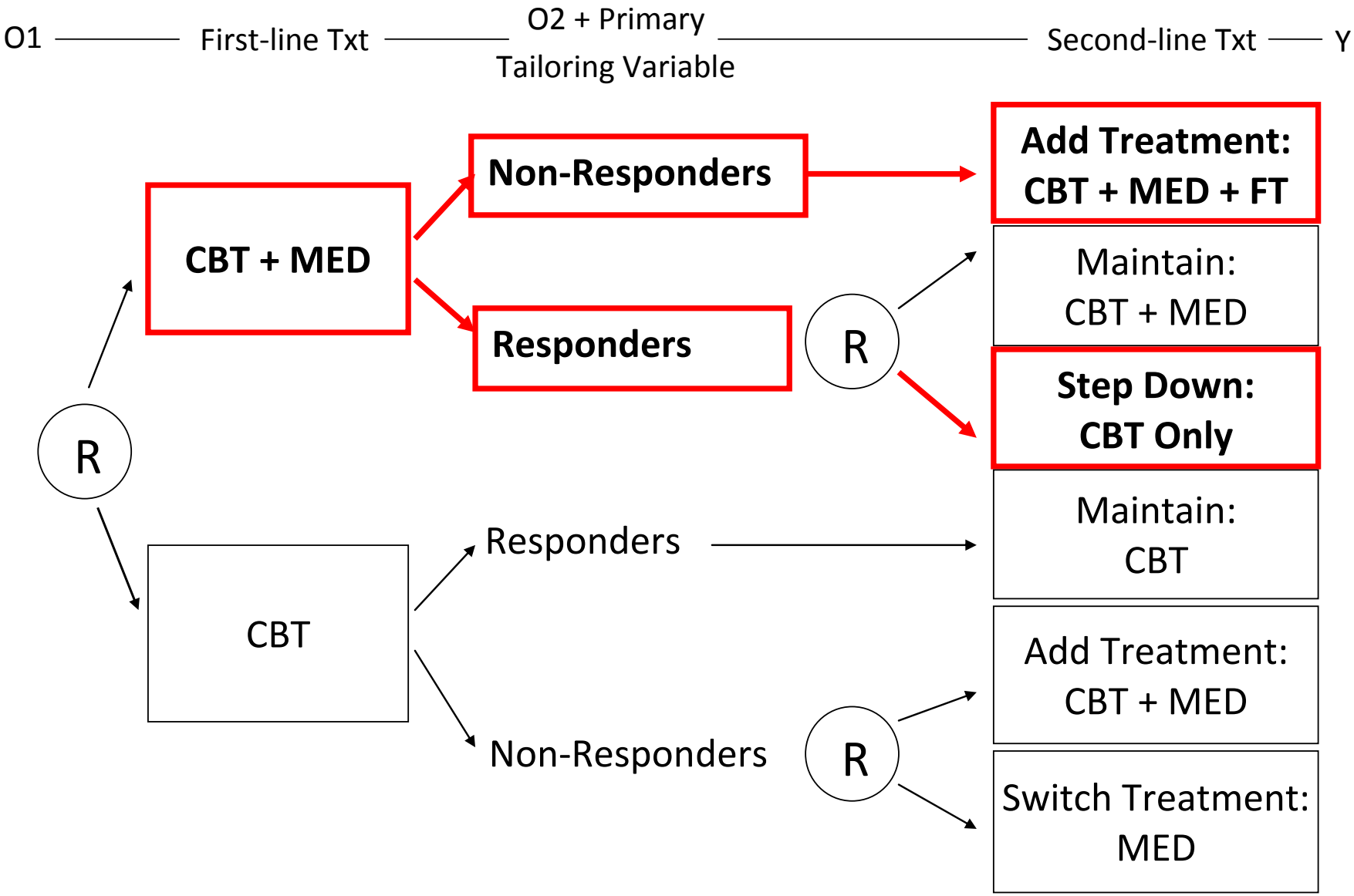
- CAMS: acute-phase, efficacy, RCT for child anxiety
- CBT+MED $>$ MED $\approx$ CBT $>$ Placebo
- However, some families and clinicians remain concerned about the use of MED in this population
- So an important next question for clinical practice is
  "Can we delay the use of MED?"
  "If so, for whom?"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

Concrete Example of a SMART: Pediatric Anxiety

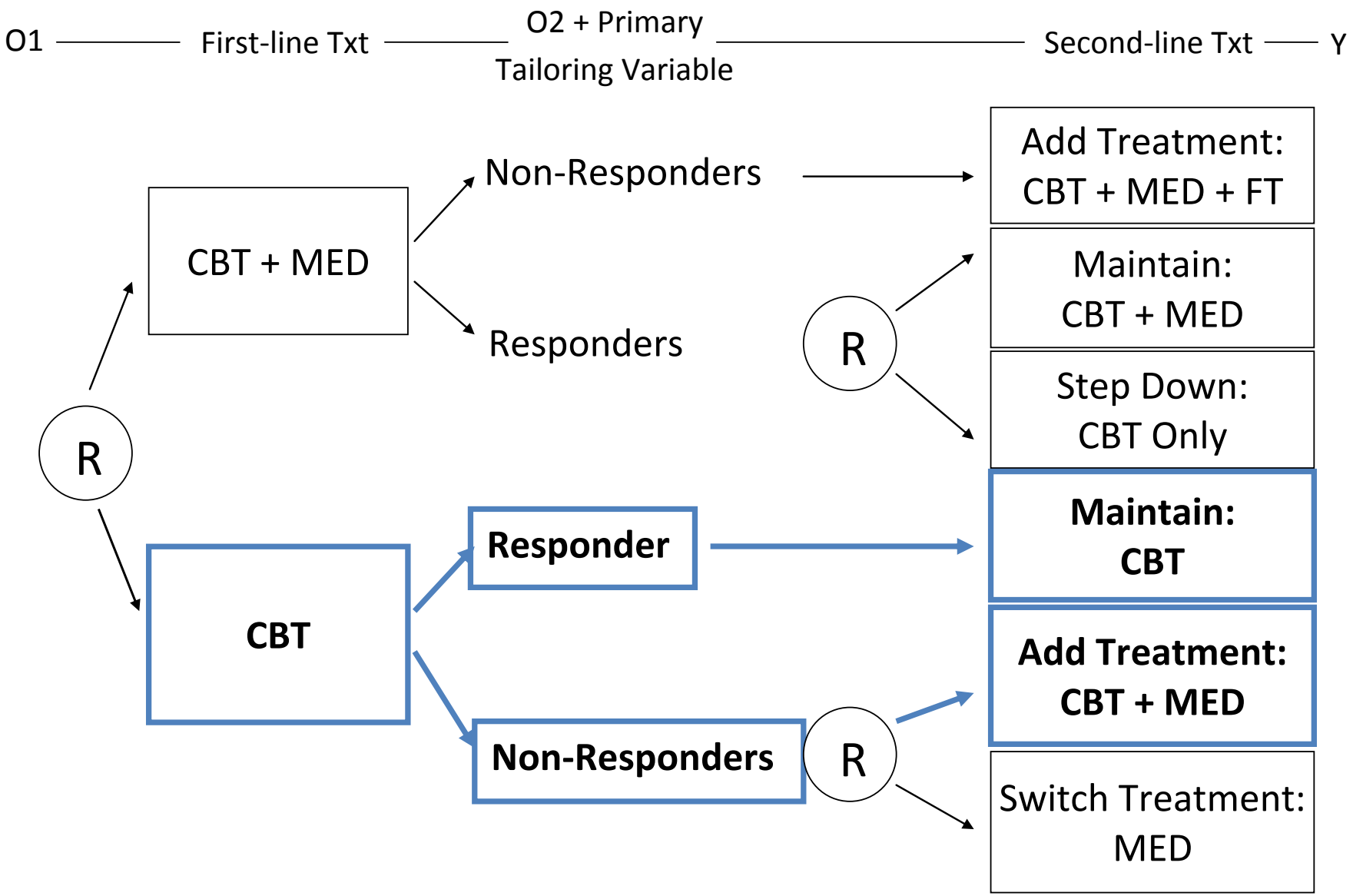
Courtesy of Scott N Compton, Duke University Medical Center



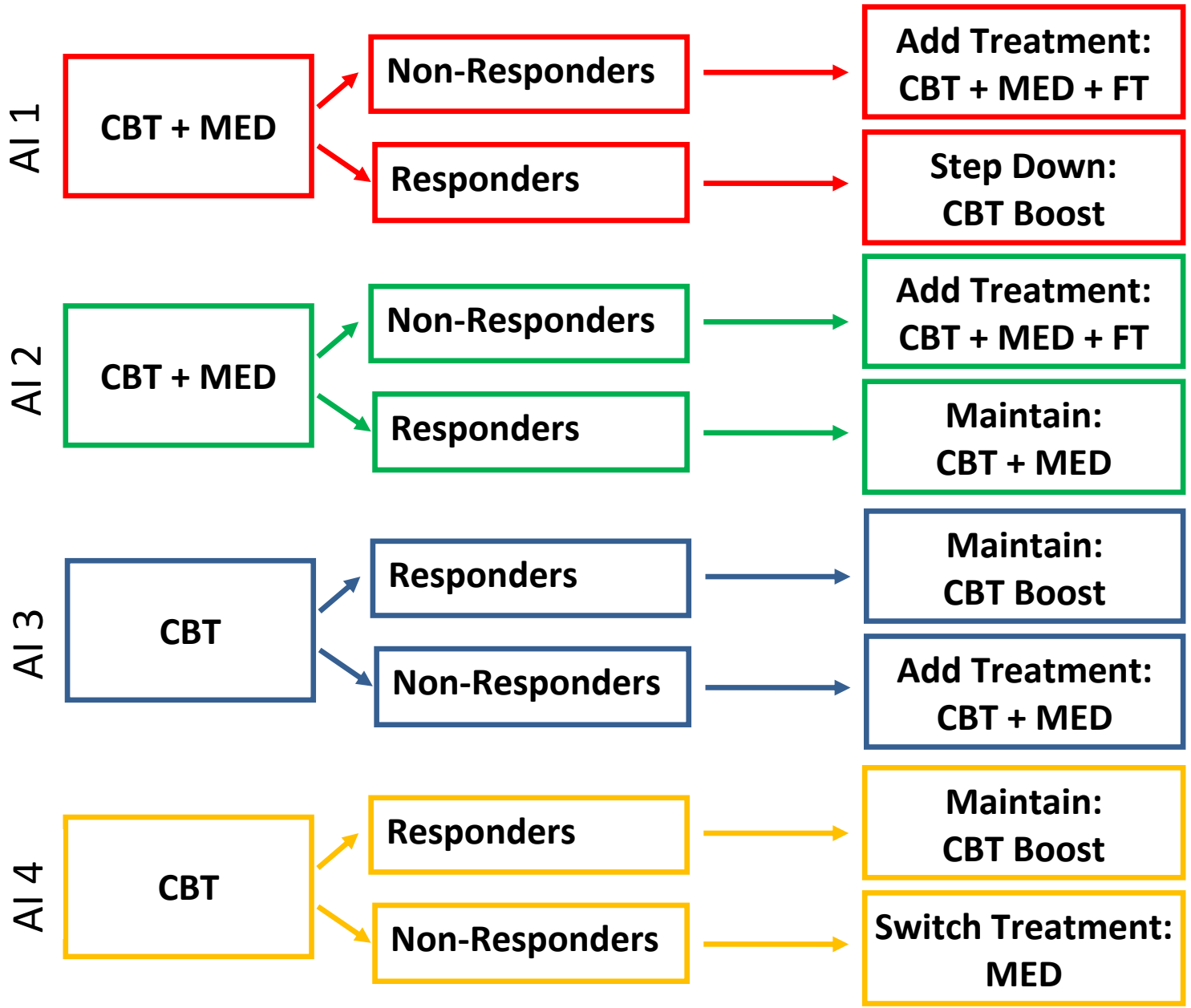
One Adaptive Intervention Within the SMART



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 simple important primary hypotheses
- Take Appropriate steps to develop a more deeply-individualized Adaptive Intervention

Keep It Simple, Straightforward

Overarching Principle

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

- Use low dimensional summary to restrict subsequent treatments
  - 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 deeply-tailored Adaptive Intervention
  - Think time-varying effect moderators

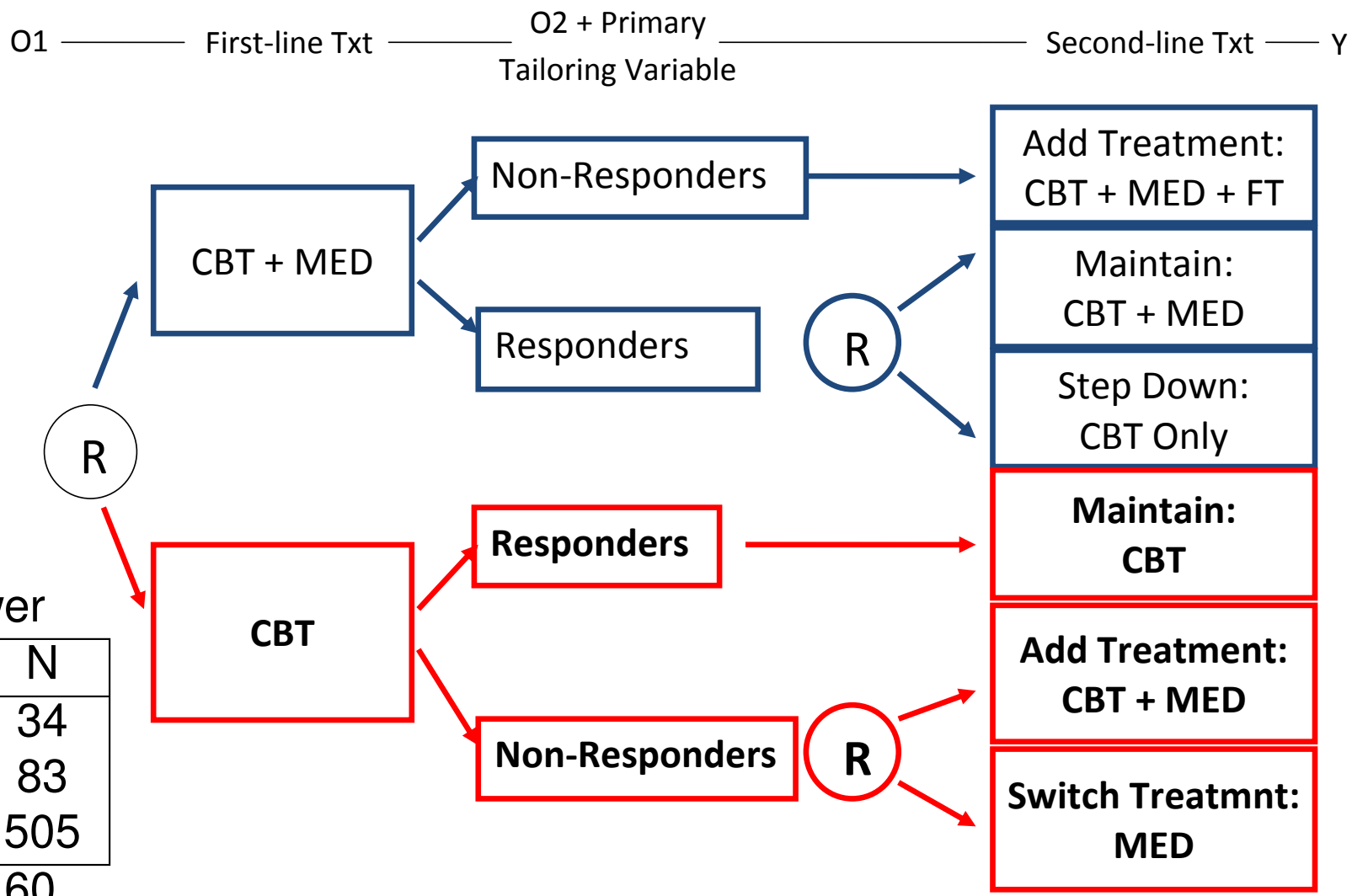
SMART Design: Primary Aims

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

Power the SMART to test this hypothesis.

Primary Aim Example 1

What is the main effect of initial CBT vs initial CBT+MED on longitudinal outcomes?



Power

ES	N
0.8	34
0.5	83
0.2	505

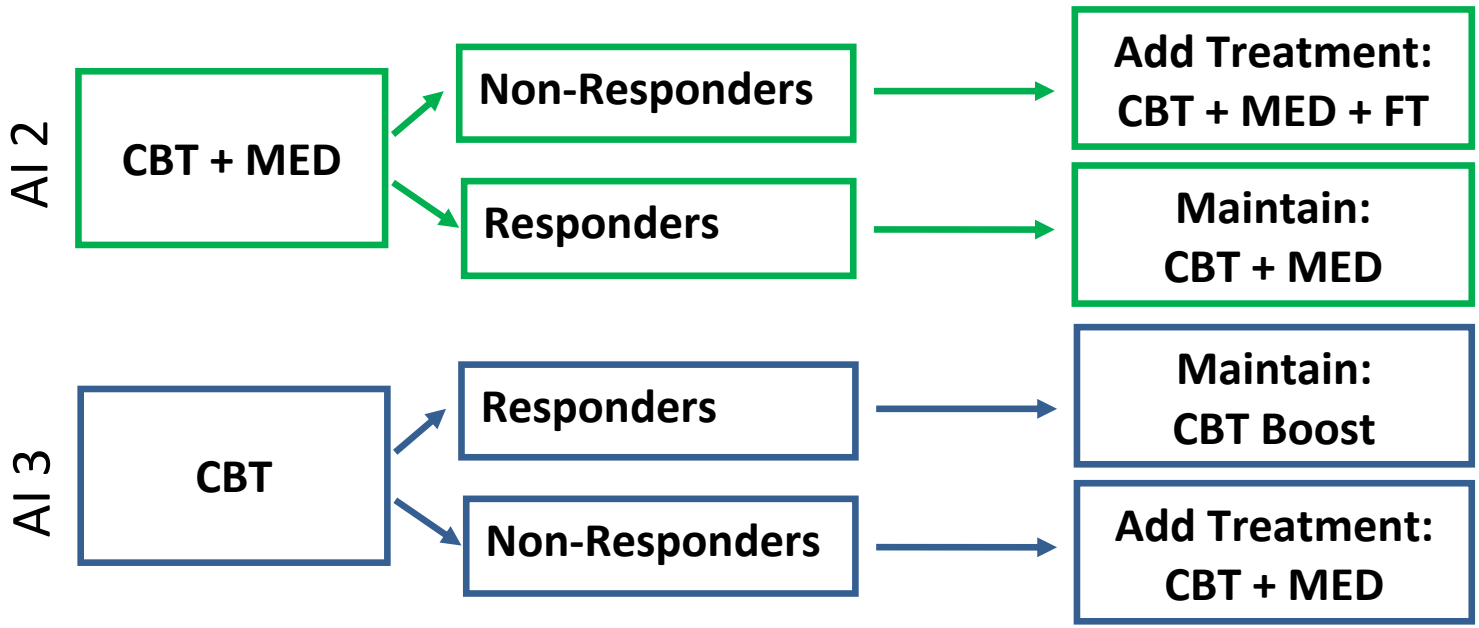
$\rho = 0.60$

$\alpha = 0.05$

$\beta = 0.20$

Primary Aim Example 2

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



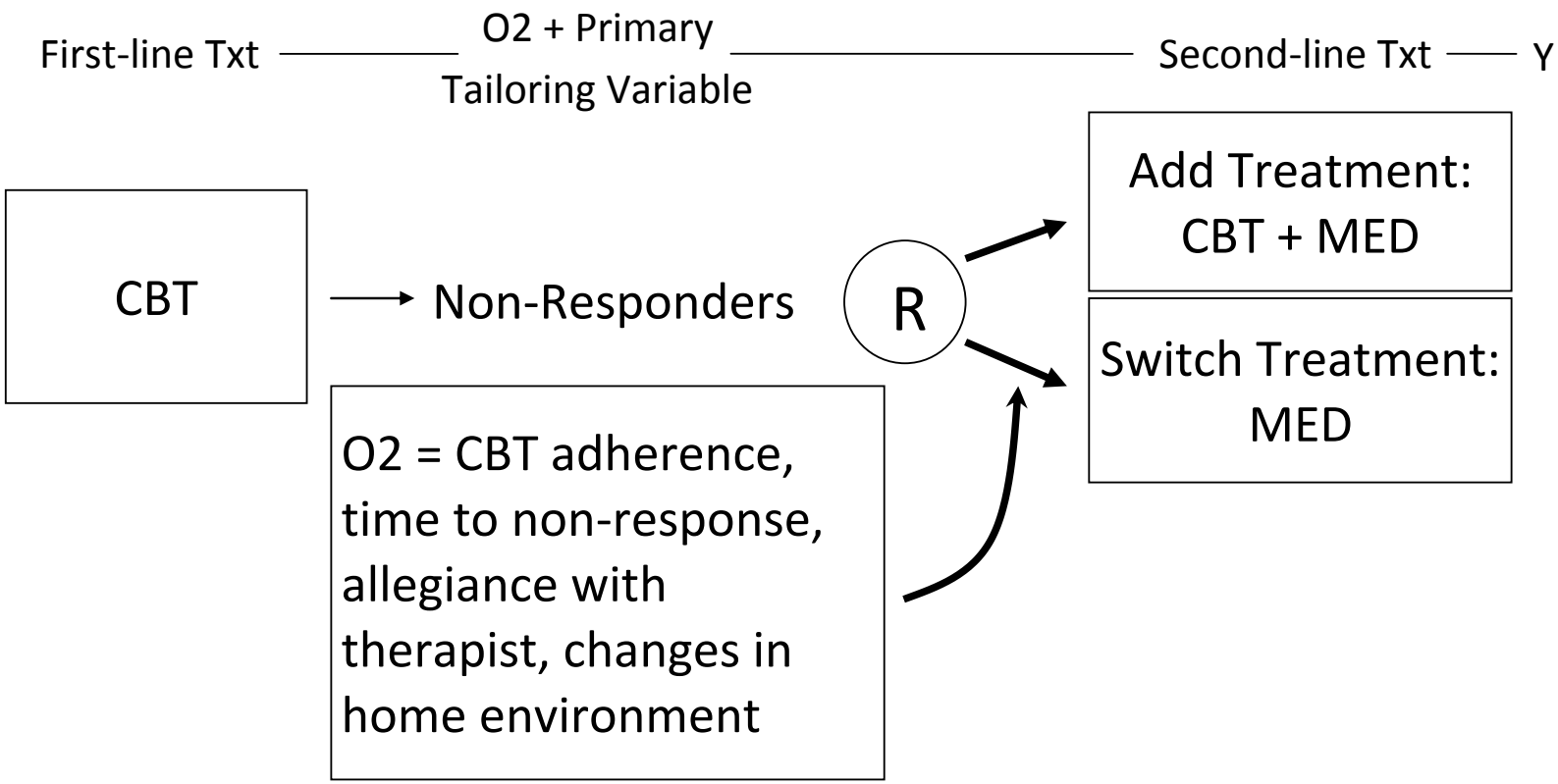
Sample size calculators exist for this; see Oetting, Levy, Weiss, and Murphy 2011.

SMART Design: Secondary Aims

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

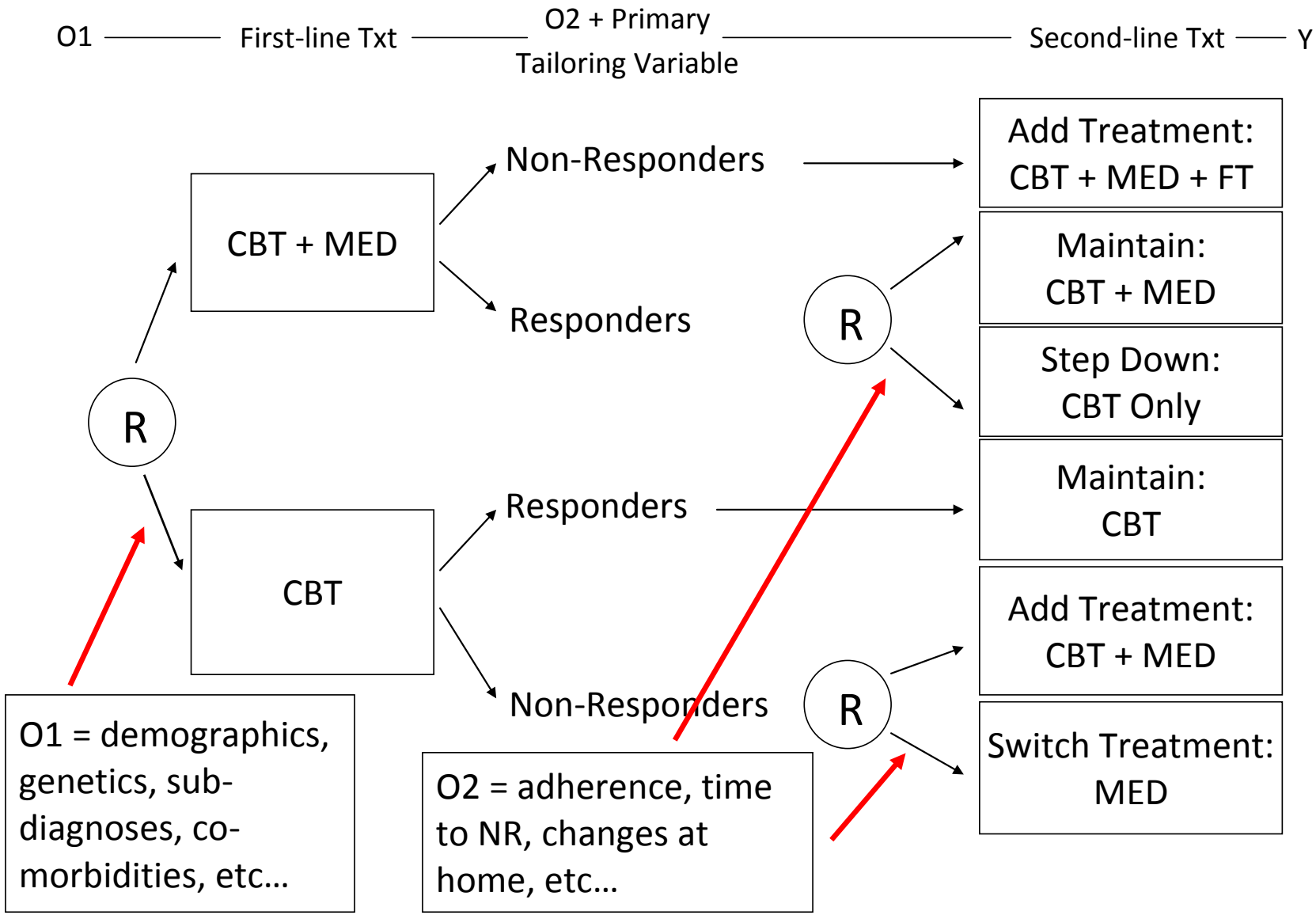
Secondary Aim Examples 1 and 2

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



Secondary Aim Example 3

Build a more deeply tailored adaptive intervention.



DISCUSSION

Adaptive Interventions vs Adaptive Experimental Designs?

- These ideas are not (necessarily) related. Confusing!

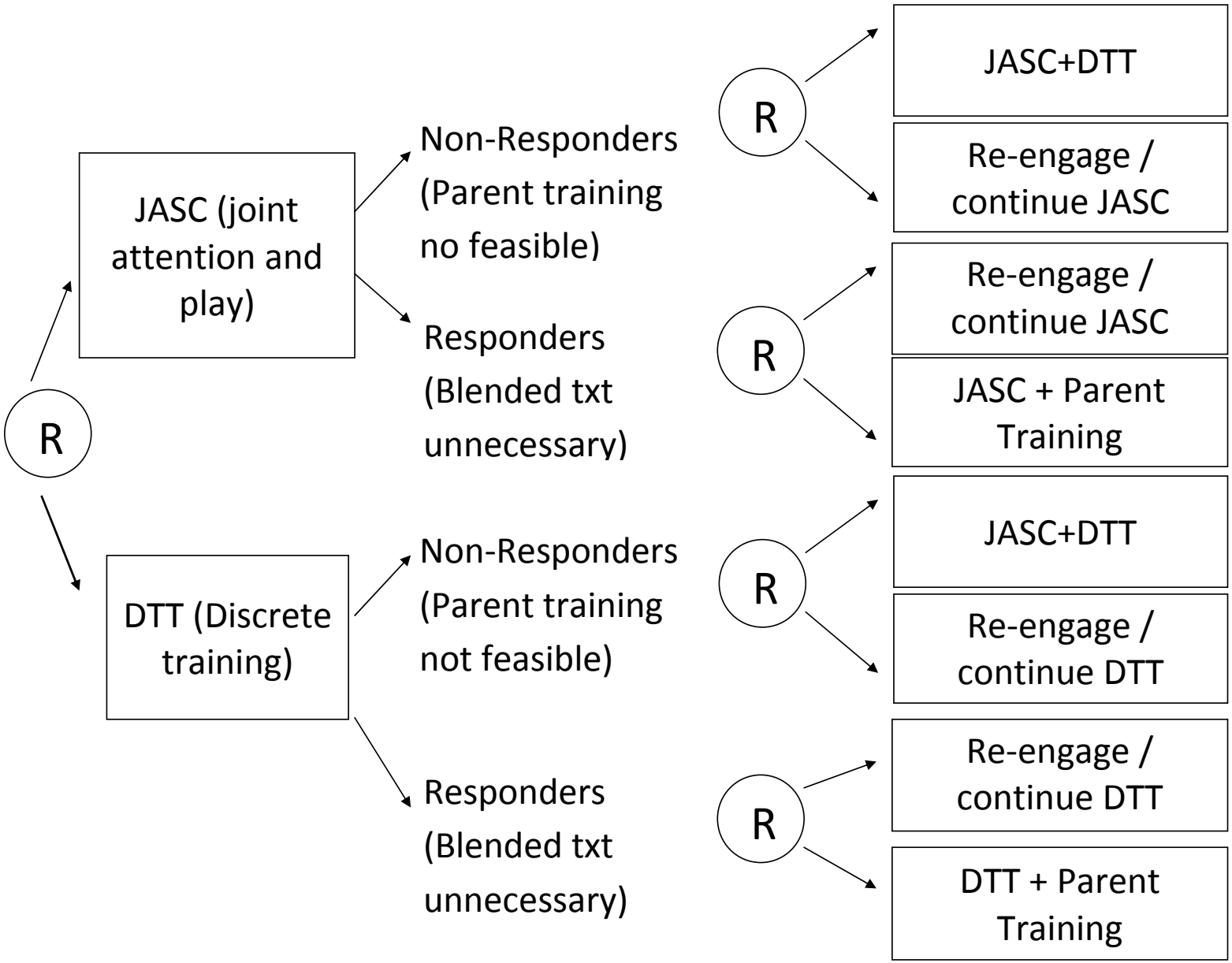
- Adaptive interventions are a type of intervention design
- Adaptive experimental designs are particular type of experimental design
- SMARTs are not Adaptive Experimental Designs
- SMARTs do inform development of Adaptive Interventions

Take Home the Following

- 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
- Existing RCTs can be used to begin to learn about adaptive interventions
  - Observational study

Interventions for Minimally Verbal Children with Autism

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



Thank you! Questions?

Find papers on SMART:

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

These slides will be posted on my website:

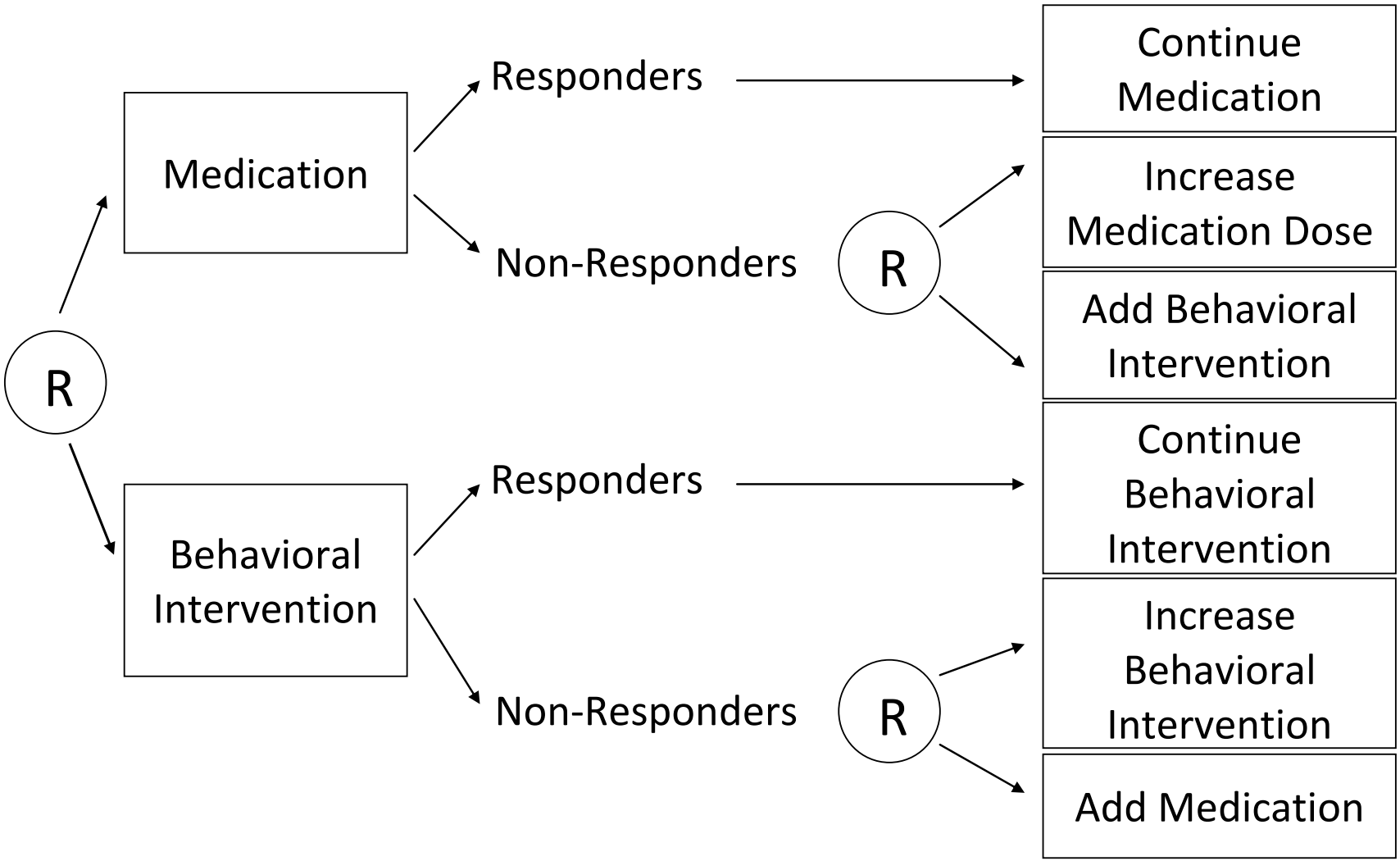
- http://www-personal.umich.edu/∼dalmiral/

Email me with questions about this presentation:

- Daniel Almirall: dalmiral@umich.edu

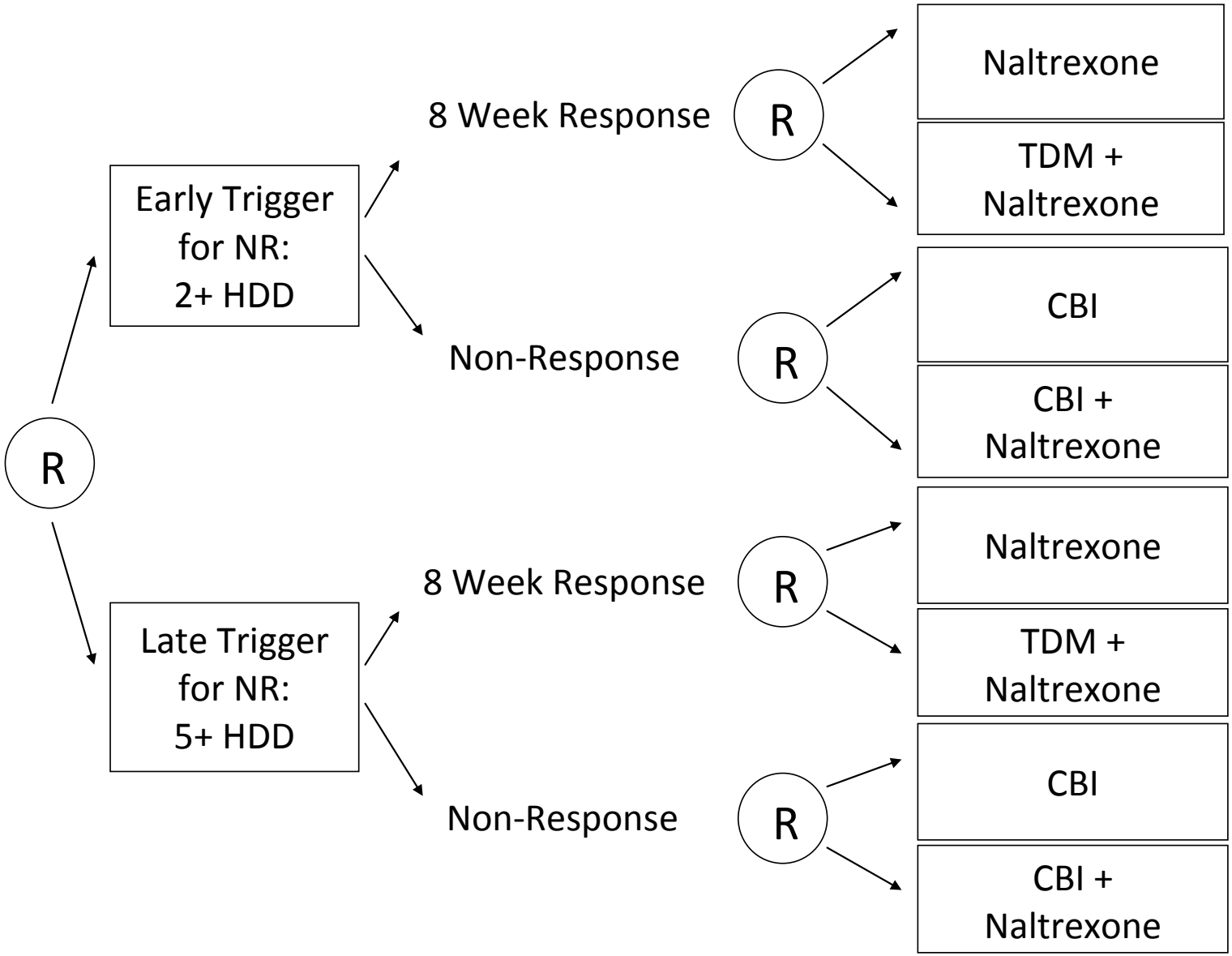
Adaptive Treatment for Children with ADHD

PI: Pelham, Florida International University



Treatment for Alcohol Dependence

PI: Oslin, University of Pennsylvania



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.